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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/US96/20766</p> <p>(22) International Filing Date: 20 December 1996 (20.12.96)</p> <p>(30) Priority Data: 60/009,192 22 December 1995 (22.12.95) US</p> <p>(71) Applicants (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). COCENSYS, INC. [US/US]; 213 Technology Drive, Irvine, CA 92618 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): BIGGE, Christopher, F. [US/US]; Apartment #6, 1856 Stadium Place, Ann Arbor, MI 48103 (US). CAI, Sui, Xiong [CN/US]; 12 Salinas, Foothill Ranch, CA 92610 (US). WEBER, Eckard [US/US]; 1290 Morningside, Laguna Beach, CA 92651 (US). WOODWARD, Richard [GB/US]; 95 Sandcastle, Aliso Viejo, CA 92656 (US). LAN, Nancy, C. [US/US]; 522 Hermosa Street, South Pasadena, CA 91030 (US). KEANA, John, F., W. [US/US]; 3854 Onyx Street, Eugene, OR 97405 (US). ZHOU, Zhang-Lin [CN/US]; 15 Bearpaw #12-</p>		<p>A, Irvine, CA 92604 (US). WRIGHT, Jonathan [GB/US]; 2311 Fernwood Avenue, Ann Arbor, MI 48104 (US).</p> <p>(74) Agents: MANDRA, Raymond, R.; Fitzpatrick, Cella, Harper &amp; Scinto, 277 Park Avenue, New York, NY 10172 (US) et al.</p> <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>
<p>(54) Title: 4-SUBSTITUTED PIPERIDINE ANALOGS AND THEIR USE AS SUBTYPE SELECTIVE NMDA RECEPTOR ANTAGONISTS</p> <p>(57) Abstract</p> <p>Novel 4-substituted piperidine analogs, pharmaceutical compositions containing the same and the method of using 4-substituted piperidine analogs as selectively active antagonists of N-methyl-D-aspartate (NMDA) receptor subtypes for treating conditions such as stroke, cerebral ischemia, central nervous system trauma, hypoglycemia, anxiety, convulsions, aminoglycoside antibiotics-induced hearing loss, migraine headaches, glaucoma, CMV retinitis, chronic pain, opioid tolerance or withdrawals, or neurodegenerative disorders, such as lathyrism, Alzheimer's Disease, Parkinsonism and Huntington's Disease are described. Also described are novel methods for preparing 4-substituted piperidine analogs and novel intermediates of the 4-substituted piperidine analogs.</p>		

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## TITLE

5           4-SUBSTITUTED PIPERIDINE ANALOGS AND THEIR  
USE AS SUBTYPE SELECTIVE NMDA RECEPTOR ANTAGONISTS

## BACKGROUND OF THE INVENTION

## 10   Field of the Invention

This invention is related to 4-substituted piperidine  
analogs, including hydroxypiperidine and  
tetrahydropyridine analogs, as well as novel  
15   intermediates of the 4-substituted analogs. The  
analogs are selectively active as antagonists of N-  
methyl-D-aspartate (NMDA) receptor subtypes. The  
invention is also directed to the use of 4-substituted  
piperidine analogs as neuroprotective agents for  
20   treating conditions such as stroke, cerebral ischemia,  
central nervous system trauma, hypoglycemia, anxiety,  
convulsions, aminoglycoside antibiotics-induced hearing  
loss, migraine headache, chronic pain, glaucoma, CMV  
retinitis, psychosis, urinary incontinence, opioid  
25   tolerance or withdrawal, or neuro-degenerative  
disorders such as lathyrism, Alzheimer's Disease,  
Parkinsonism and Huntington's Disease.

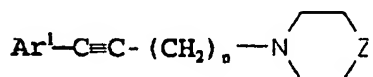


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## Related Background Art

Excessive excitation by neurotransmitters can cause the degeneration and death of neurons. It is believed that this degeneration is in part mediated by the excitotoxic actions of the excitatory amino acids (EAA) glutamate and aspartate at the N-methyl-D-Aspartate (NMDA) receptor. This excitotoxic action is considered responsible for the loss of neurons in cerebrovascular disorders such as cerebral ischemia or cerebral infarction resulting from a range of conditions, such as thromboembolic or hemorrhagic stroke, cerebral vasospasms, hypoglycemia, cardiac arrest, status epilepticus, perinatal asphyxia, anoxia such as from drowning, pulmonary surgery and cerebral trauma, as well as lathyrism, Alzheimer's Disease, Parkinson's Disease and Huntington's Disease.

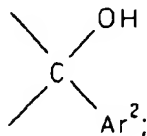
Various classes of substituted piperidine analogs are known. For example, U.S. Patent No. 5,273,977 generically discloses tetrahydropyridine and hydroxy piperidine derivatives described by the formula:



wherein n is an integer of 2, 3, or 4; Z is



or

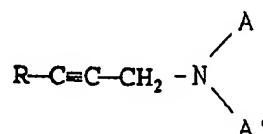


Ar<sup>1</sup> and Ar<sup>2</sup> are each independently substituted or unsubstituted aryl, a heteroaromatic ring, or a heteroaromatic bicyclic ring. The tetrahydropyridines

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and hydroxypiperidines of this reference are indicated to be useful as central nervous system agents, particularly as dopaminergic, antipsychotic and antihypertensive agents, and for treating central nervous system disorders such as Parkinson Disease, Huntington Disease and depression. The particular 4-substituted piperidines, including the 4-hydroxypiperidines and tetrahydropyridines of this invention are not exemplified. In addition, there is no disclosure or suggestion of treating disorders with selective NMDA receptor subtype antagonists and the advantages of such treatment.

GB 1055548 discloses 1-aryl-3-aminopropynes having the generic formula:



wherein R represents unsubstituted phenyl or phenyl substituted by methyl, halogen, nitro, amino, (lower alkanoyl)amino, or lower alkoxy; and either A is alkyl of 1 to 4 carbon atoms and A' is alkyl of 1 to 4 carbon atoms, benzyl, chlorobenzyl, or dimethoxybenzyl; or A and A', together with the adjacent nitrogen atom, from one of the following heterocyclic rings: pyrrolidino, morpholino, thiomorpholino, 4-phenylpiperidino, 4-phenyl-4-hydroxypiperidino, N'-methylpiperazino, N'-benzylpiperazino, N'-phenylpiperazino, N'-chlorophenylpiperazino, N'-tolylpiperazino, N'-methoxyphenylpiperamino, N'-( $\beta$ -hydroxyethyl)-piperazino, N'-( $\beta$ -acetoxyethyl)piperazino, N'-( $\beta$ -propionyloxyethyl)-piperazino, N'-carbethoxypiperazino, hexamethyleneimino, and heptamethylene-imino; provided that when R is phenyl, p-methoxyphenyl, o- or

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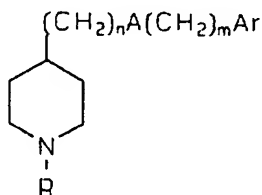
p-nitrophenyl, or o-aminophenyl,  $\begin{array}{c} \diagup A \\ -N \\ \diagdown A' \end{array}$  does not

represent dimethylamino or diethylamino; and their acid addition salts, especially those containing physiologically innocuous anions. The compounds of this reference are said to have antiulcer activity. This reference does not disclose or suggest the 4-substituted piperidine analogs of this invention or their use as selective NMDA receptor subtype antagonists.

10

DE 3703435 discloses compounds having a piperidine ring substituted by an aminothiazole moiety. The compounds are said to be useful for treating Parkinson's Disease, schizophrenia and circulatory disorders with a particular effect on the dopaminergic system. This reference does not disclose or suggest the compositions of the present invention, let alone their use as selective NMDA receptor subtype antagonists.

20 PCT International Publication Number WO 92/02502 generically discloses N-hydrocarbyl 4-substituted piperidines described by the formula:



25

in which

R is C<sub>1-8</sub>alkyl(phenyl)p, C<sub>2-8</sub>alkenyl(phenyl)p,  
C<sub>2-8</sub>alkynyl(phenyl)p, C<sub>3-8</sub>cycloalkyl;

p is 0 to 2;

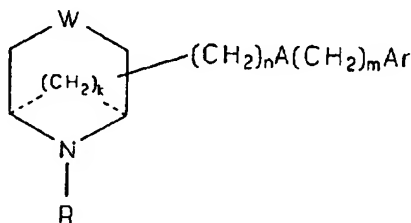
30 n is 0 to 6;

- 5 -

- A is a bond, oxygen, sulphur or  $\text{NR}^1$ ;  
 $\text{R}^1$  is hydrogen,  $\text{C}_{1-8}$ alkyl or phenyl $\text{C}_{1-4}$ alkyl;  
 m is 0 to 3; and  
 Ar is aryl or heteroaryl, each of which may be  
 5 optionally substituted; and salts thereof.

This reference exemplifies 4-aryloxyalkyl piperidines.  
 The substituted piperidines are said to be calcium  
 channel blockers expected to be useful in the treatment  
 10 of anoxia, ischemia including stroke, migraine,  
 epilepsy, traumatic head injury, AIDS-related dementia,  
 neurodegenerative disorders and drug addiction. The  
 reference does not disclose or suggest the particular  
 4-substituted piperidine analogs of this invention or  
 15 their use as selective NMDA receptor subtype  
 antagonists for the treatment of disorders responsive  
 thereto.

PCT International Publication Number WO 93/15052  
 20 generically describes compounds that are said to be  
 calcium channel antagonists broadly represented by the  
 formula:



- 25 and the salts thereof, wherein W is  $-\text{CH}_2-$ , a bond, O or  
 S; k is 0, or when W represents  $-\text{CH}_2-$  k may also be 2,  
 in which case the dotted lines represent single bonds;  
 R is  $\text{C}_{1-8}$ alkyl(phenyl)p,  $\text{C}_{2-8}$ alkenyl(phenyl)p,  
 30  $\text{C}_{2-8}$ alkynyl(phenyl)p,  $\text{C}_{3-8}$ cycloalkyl or  
 $\text{C}_{1-8}$ alkyl $\text{C}_{3-8}$ cycloalkyl, or R may also represent hydrogen  
 when k is 2; p is 0 to 2  
 n is 0 to 6;

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m is 0 to 6; and  
A is a bond, -CH=CH-, -C=C-, oxygen, sulphur or NR<sup>1</sup>;  
R<sup>1</sup> is hydrogen, C<sub>1-8</sub>alkyl or phenylC<sub>1-4</sub>alkyl; and  
Ar is aryl or heteroaryl, each of which may be  
5 optionally substituted; provided that: when W is a  
bond the side chain is  $\alpha$  to the ring nitrogen atom;  
when W is CH<sub>2</sub>, k is zero, the side chain is at the 3- or  
4-position of the piperidine ring and A is a bond,  
oxygen, sulphur or NR<sup>1</sup> then Ar is aryl substituted by  
10 phenoxy or substituted phenoxy or is a tricyclic  
heteroaryl group as hereinafter defined; and when W is  
CH<sub>2</sub> and k is 2 the side chain -(CH<sub>2</sub>)<sub>k</sub>A(CH<sub>2</sub>)<sub>m</sub>Ar is not  $\alpha$   
to the nitrogen atom. This reference exemplifies  
mostly 2 and 3 substituted piperidines. In addition,  
15 the particular group of 3 and 4 substituted piperidines  
described by the reference requires A to be -CH=CH- or  
-C=C-. This reference does not disclose or suggest the  
4-substituted piperidine analogs of this invention.  
Moreover, there is no suggestion of employing 4-  
20 substituted piperidine analogs as selective NMDA  
receptor subtype antagonists.

EP 0235463 discloses N-substituted-arylalkyl and  
arylalkylene aminoheterocyclics as coronary  
25 vasodilators, antihypertensives, antiarrhythmic,  
antiallergy, antihistamic and antisecretory agents. 4-  
substituted N-alkene and alkyne piperidine analogs of  
this invention, as well as their NMDA antagonistic  
activity, are not disclosed or suggested.

30 U.S. Patent No. 5,169,855 generically discloses  
disubstituted piperidine ether derivatives for use as  
antipsychotic agents selective for sigma receptors.  
Similarly, PCT International Publication No.  
35 WO 92/18127 and PCT International Publication No.  
WO 91/06297 generically disclose N-phthalimidoalkyl  
piperidines which are useful as antipsychotic agents

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and which are selective for sigma receptors. However, the 4-substituted piperidine analogs of this invention are not disclosed by these references and there is no mention of NMDA receptor activity.

5

Numerous references have disclosed additional piperidine derivatives substituted at the 4 and 3 position for use in a variety of treatments. Such references include, for example, U.S. Patent No. 10 3,255,196 (3 and 4-substituted piperidines that are active antitussives and possess analgesic, antiemetic and local anaesthetic properties); U.S. Patent No. 5,202,346 (4-substituted piperidines that are Class III antiarrhythmic agents); PCT International Publication 15 No. WO 88/02365 (3 and 4-substituted piperidines that may be useful for treatment of mental disorders accompanying cerebrovascular disease); BE 860701 (4-substituted piperidines for use as vasodilators and  $\beta$ -adrenergic inhibitors); FR 2681319 (4-substituted 20 piperidines for use as neuroprotectors and anticonvulsants); and DE 2939292 (4-substituted piperidines for use as antiallergenic and antiinflammatory agents). None of these references disclose or suggest the 4-substituted piperidine 25 analogs of the present invention or their use as selective NMDA receptor subtype antagonists.

Excitatory amino acid receptor antagonists that block NMDA receptors are recognized for usefulness in the 30 treatment of disorders. NMDA receptors are intimately involved in the phenomenon of excitotoxicity, which may be a critical determinant of outcome of several neurological disorders. Disorders known to be responsive to blockade of the NMDA receptor include 35 acute cerebral ischemia (stroke or cerebral trauma, for example), muscular spasm, convulsive disorders, neuropathic pain and anxiety, and may be a significant

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causal factor in chronic neurodegenerative disorders such as Parkinson's disease [T. Klockgether, L. Turski, Ann. Neurol. 34, 585-593 (1993)], human immunodeficiency virus (HIV) related neuronal injury, amyotrophic lateral sclerosis (ALS), Alzheimer's disease [P.T. Francis, N.R. Sims, A.W. Procter, D.M. Bowen, J. Neurochem. 60 (5), 1589-1604 (1993)] and Huntington's disease. [See S. Lipton, TINS 16 (12), 527-532 (1993); S.A. Lipton, P.A. Rosenberg, New Eng. J. Med. 330 (9), 613-622 (1994); and C.F. Bigge, Biochem. Pharmacol. 45, 1547-1561 (1993) and references cited therein.]. NMDA receptor antagonists may also be used to prevent tolerance to opiate analgesia or to help control withdrawal symptoms from addictive drugs (Eur. Pat. Appl. 488,959A).

Expression cloning of the first NMDA receptor subunit, NMDAR1 (NR1) in Nakanishi's lab in 1991 provided an initial view of the molecular structure of the NMDA receptor [Nature 354, 31-37 (1991)]. There are several other structurally related subunits (NMDAR2A through NMDAR2D) that join NR1 in heteromeric assemblies to form the functional ion channel complex of the receptor [Annu. Rev. Neurosci. 17, 31-108 (1994)]. The molecular heterogeneity of NMDA receptors implies a future potential for agents with subtype selective pharmacology.

Many of the properties of native NMDA receptors are seen in recombinant homomeric NR1 receptors. These properties are altered by the NR2 subunits. Recombinant NMDA receptors expressed in *Xenopus* oocytes have been studied by voltage-clamp recording, as has developmental and regional expression of the mRNAs encoding NMDA receptor subunits. Electrophysiological assays were utilized to characterize the actions of compounds at NMDA receptors expressed in *Xenopus*

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oocytes. The compounds were assayed at three subunit combinations of cloned rat NMDA receptors, corresponding to four putative NMDA receptor subtypes [Moriyoshi, et al. Nature 1991, 354, 31-37; Monyer et al, Science 1992, 256, 1217-1221; Kutsuwada et al, Nature 1992, 358, 36-41; Sugihara et al, Biochem. Biophys Res. Commun. 1992, 185, 826-832].

An object of this invention is to provide novel 4-substituted piperidine analogs which function as subtype-selective NMDA receptor antagonists.

A further object of this invention is to provide a pharmaceutical composition containing an effective amount of the 4-substituted piperidine analogs to treat cerebrovascular disorders responsive to the selective blockade of NMDA receptor subtypes.

Another object of this invention is to provide a method of treating disorders responsive to the subtype-selective NMDA receptor antagonists in an animal by administering a pharmaceutically effective amount of 4-substituted piperidine analogs.

Yet another object of this invention is to provide novel methods of preparing 4-substituted piperidine analogs.

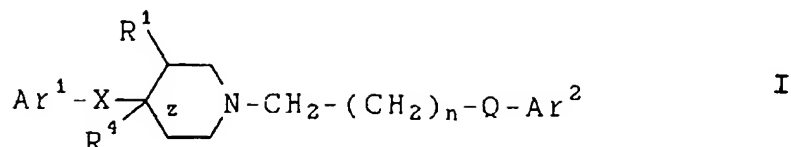
A further object of this invention is directed to novel intermediates of the 4-substituted piperidine analogs of this invention.

#### SUMMARY OF THE INVENTION

This invention relates to novel 4-substituted piperidine analogs represented by the formula (I):



- 10 -



or a pharmaceutically acceptable salt thereof wherein

- 5 Ar<sup>1</sup> and Ar<sup>2</sup> are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an
- 10 alkylguanidine group, a lower alkyl amino group or a lower alkoxy group;

z is a single or double bond;

- 15 X is -(CHR<sup>2</sup>)<sub>m</sub>-, O, S or NR<sup>3</sup>, wherein each R<sup>2</sup> is independently hydrogen, hydroxy, lower alkoxy or a lower alkyl group having 1 to 6 carbon atoms and m is 0, 1 or 2, and R<sup>3</sup> is hydrogen or a lower alkyl group having 1 to 6 carbon atoms, provided that when z is a
- 20 double bond then X is not O, S or NR<sup>3</sup>;

R<sup>1</sup> is hydrogen or hydroxy;

n is 0, 1 or 2;

25

Q is -CH=CH- or -C≡C-; and

R<sup>4</sup> is hydrogen or hydroxy when z is a single bond

- 30 provided that (i) when n is 0, then z is a double bond and R<sup>4</sup> is not present, (ii) when n is 1 or 2 and Q is -C≡C- and z is a double bond or R<sup>4</sup> is hydroxy, then Ar<sup>1</sup> is aryl substituted by halogen and (iii) when R<sup>4</sup> is hydroxy then R<sup>2</sup> is not hydroxy or lower alkoxy.

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The compounds of the present invention may exist as optical isomers and the inventive compounds include both the racemic mixtures of such optical isomers as well as the individual enantiomers.

5

Examples of pharmaceutically acceptable addition salts include inorganic and organic acid addition salts such as the hydrochloride, hydrobromide, phosphate, sulphate, citrate, lactate, tartrate, maleate, fumarate, mandelate, oxalate, and the acetate.

Halogen is fluorine, chlorine, bromine, or iodine; fluorine, chlorine, and bromine are preferred groups.

15 Alkyl means a straight or branched chain of from one to six carbon atoms or cyclic alkyl of from three to seven carbon atoms including, but not limited to methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

Aryl means a monocyclic or bicyclic carbocyclic aromatic ring system which can be substituted or unsubstituted, for example, but not limited to phenyl, naphthyl or the like.

Heteroaryl means a monocyclic or bicyclic carbocyclic aromatic ring system substituted by one or more hetero atoms, which can be the same or different, and includes, for example, thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranal, isobenzofuranyl, chromenyl, xanthenyl, phenoxanthiaryl, 2H-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizaryl, isoindolyl, 3H-indolyl, indolyl, indazolyl, purinyl, 4H-quinolizaryl, isoquinolyl, quinolyl, phthalzaryl, naphthyridinyl, quinoxalinyl, cinnolinyl, pteridinyl,

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5aH-carbozoly1, carbozoly1,  $\beta$ -carboliny1,  
phenanthridiny1, acrindiny1, perimidiny1,  
phenanthroliny1, phenaziny1, isothiazoly1,  
phenothiaziny1, isoxazoly1, furazany1, phenoxaziny1,  
5 quinoxaliny1, 2,3-dioxoquinoxaliny1, benzimidazoly1, 2-  
oxobenzimidazoly1, 2-oxindoly1 and 2-thiobenzimidazoly1  
groups.

Aralkyl means any of the alkyl groups defined herein  
10 substituted by any of the aryl groups as defined  
herein.

Halogenated alkyl means any of the alkyl groups defined  
herein substituted by one or more halogen groups as  
15 defined herein.

Alkylguanidine means a guanidine substituted by one of  
the alkyl groups defined herein.

20 Lower alkyl amino means any of the alkyl groups defined  
herein substituted by an amino group.

Lower alkoxy means an alkoxy group containing an alkyl  
group as defined herein.

25

The instant invention is also related to a  
pharmaceutical composition containing the compound  
defined by formula I in an amount effective to treat  
cerebrovascular disorders responsive to the selective  
30 blockade of NMDA receptor subtypes and a  
pharmaceutically acceptable carrier. Exemplary  
disorders responsive to such treatment include cerebral  
ischemia caused by cerebral trauma, stroke,  
hypoglycemia, heart attack, and surgery; anxiety,  
35 psychosis and schizophrenia; glaucoma; CMV retinitis;  
urinary incontinence; opioid tolerance or withdrawal;  
and chronic neurodegenerative disorders such as

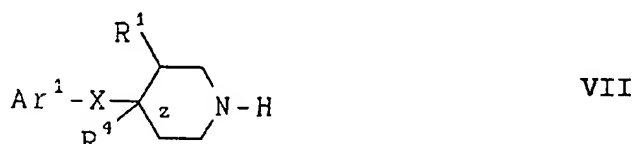
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Huntington's disease, ALS, Parkinsonism and Alzheimer's disease. The pharmaceutical composition of this invention may also be employed as an analgesic or for the treatment of epilepsy or migraine headaches.

5

The invention is also related to a method for preparing the compound of formula (I) comprising the steps of:

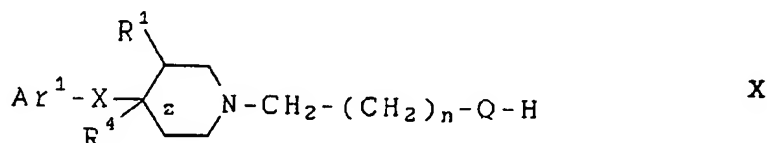
(a) reacting, in the presence of a base, a compound of  
10 formula VII



wherein Ar<sup>1</sup>, X, R<sup>1</sup>, R<sup>4</sup> and z are as previously described,  
15 with a compound of formula IX



wherein n and Q are as previously described and L is a  
20 leaving group to afford a compound of formula X



wherein Ar<sup>1</sup>, X, R<sup>1</sup>, R<sup>4</sup>, z, n and Q are as previously  
25 described; and

(b) reacting the compound of formula X with Ar<sup>2</sup>Y,  
wherein Ar<sup>2</sup> is as previously defined and Y is a  
transmetalation group, such as for example, Br, I,  
30 B(OH)<sub>3</sub>, or HgCl<sub>2</sub>, in the presence of a palladium catalyst  
to afford the compound of formula I. The leaving group  
L is preferably selected from the group consisting of  
para-toluenesulfonate, halogen, triflate and the like.

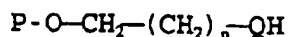
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Para-toluenesulfonate is most preferred. The transmetalation group is a group capable of transmetalating with palladium.

- 5 The base used in step (a) of the above described process is generally present in at least an amount equivalent to the tosylate of formula IX to ensure that the tosic acid evolved during the reaction is quenched. Such bases include, for example, triethylamine,  
10 potassium carbonate or the like. The reaction of step (a) is conducted in a polar aprotic solvent, such as, for example, tetrahydrofuran, dimethylformamide, acetonitrile or the like. The reaction generally may be conducted at temperature between ambient temperature  
15 and 100°C, although the temperature is typically not critical.

- The reaction of step (b) is conducted typically in the presence of a palladium catalyst such as  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  
20 i.e., bis(triphenyl-phosphine)palladium(II)chloride and a base such as, for example, triethylamine. The reaction of this step is generally run at a temperature from about 60 to about 100°C in a polar solvent such as tetrahydrofuran, methanol, acetonitrile, t-butylamine  
25 or the like. The resulting product may be purified by means well known to those of ordinary skill in the art.

- Yet another method of this invention for preparing the compound of formula (I) comprises the steps of: (a)  
30 reacting, in the presence of a palladium catalyst, a compound of formula XI

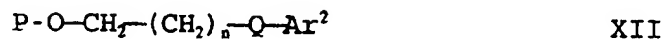


XI

- 35 wherein P is a general protecting group, and n and Q are as previously described, with  $\text{Ar}^2\text{Y}$ , wherein  $\text{Ar}^2$  is as previously defined and Y is a transmetalating group,

- 15 -

such as for example Br, I, B(OH)<sub>2</sub> or HgCl<sub>2</sub>, to afford a compound represented by formula XII



5

wherein P, n, Q and Ar<sub>2</sub> are as previously described;

(b) deprotecting the compound of formula XII to give a compound represented by formula XIII

10



wherein n, Q and Ar<sup>2</sup> are as previously described;

(c) reacting the compound of formula XIII with an activating compound such as tosylates e.g., tosylchloride, mesylates triflates, diethylazadicarboxylates or the like in the presence of base, to give the compound represented by formula XIV

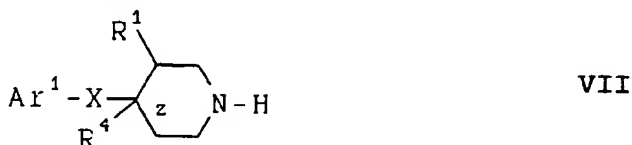
20



wherein A is an activating group such as, for example, a para-toluenesulfonate group, and n, Q and Ar<sup>2</sup> are as previously described; and

25

(d) reacting, in the presence of a base, the compound of formula XIV with the compound of formula VII



30

wherein Ar<sup>1</sup>, X, R<sup>1</sup>, R<sup>4</sup> and z are as previously described, to give the compound of formula I.

The general protecting group P of this method of the invention is, for example, selected from the group

35

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consisting t-butyldimethylsilyl, methoxymethyl, tetrahydropyranyl, trimethylsilyl and the like, with the silyl protecting groups preferred. The palladium catalyst employed in step (a) of this method may be, for example,  $\text{PdCl}_2(\text{PPh}_3)_2$ . Generally this step of the reaction is conducted in the presence of a base, such as triethylamine, at a temperature range of 60-100°C in a polar solvent, such as tetrahydrofuran, methanol, acetonitrile, t-butylamine or the like.

10

Step (d) of this method is also performed in the presence of a base, such as triethylamine or potassium carbonate, to ensure that the toxic acid evolved during the reaction is quenched. This reaction step (d) is performed in an aprotic polar solvent, such as tetrahydrofuran, dimethylformamide, acetonitrile or the like at a temperature typically between ambient temperature and about 100°C. The resulting product may be purified by means well known to one of ordinary skill in the art.

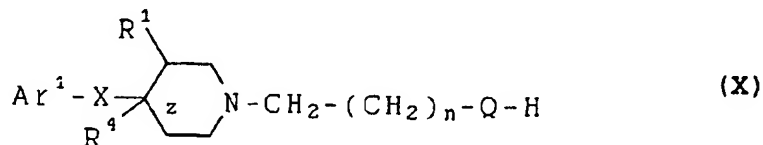
20

This invention is further directed to novel intermediates which may be prepared during the preparation of the 4-substituted piperidine analogs of this invention. These novel intermediates also possess NMDA subtype selective activity.

25

The novel intermediate compounds are represented by the formula (X):

30



or a salt thereof, wherein

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Ar<sup>1</sup> is aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>,  
 5 -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, a lower alkyl amino group or a lower alkoxy group;

z is a single or double bond;

10 X is -(CHR<sup>2</sup>)<sub>m</sub>-, O, S or NR<sup>3</sup>, wherein each R<sup>2</sup> is independently hydrogen, hydroxy, lower alkoxy or a lower alkyl group having 1 to 6 carbon atoms and m is 0, 1 or 2, and R<sup>3</sup> is hydrogen or a lower alkyl group having 1 to 6 carbon atoms, provided that when z is a  
 15 double bond then X is not O, S or NR<sup>2</sup>;

Q is -CH=CH- or -C≡C-;

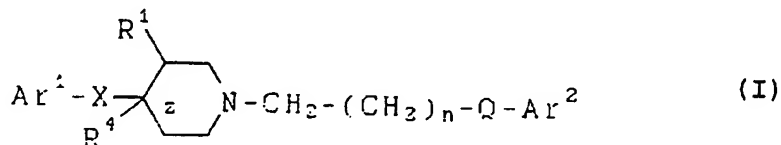
R<sup>1</sup> is hydrogen or hydroxy; and

20

R<sup>4</sup> is hydrogen or hydroxy when z is a single bond, provided that (i) when X is -(CHR<sup>2</sup>)<sub>m</sub>-, m is 0 and Q is -C≡C- then z is not a double bond and (ii) when R<sup>4</sup> is hydroxy then R<sup>2</sup> is not hydroxy or lower alkoxy.

25

The invention further relates to a method for treating disorders responsive to the selective blockade of N-methyl-D-aspartate receptor subtypes in an animal suffering thereof which comprises administering in unit  
 30 dosage form at least one compound represented by the formula (I):



or a pharmaceutically acceptable salt thereof wherein

35



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Ar<sup>1</sup> and Ar<sup>2</sup> are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, alkyl, halogen, hydroxy, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, 5 -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an alkylguanidine group, a lower alkyl amino group or a lower alkoxy group;

z is a single or double bond;

10

X is -(CHR<sup>2</sup>)<sub>m</sub>-, O, S or NR<sup>3</sup>, wherein R<sup>2</sup> is independently hydrogen, hydroxy, lower alkoxy or a lower alkyl group having 1 to 6 carbon atoms and m is 0, 1 or 2, and R<sup>3</sup> is 15 hydrogen or a lower alkyl group having 1 to 6 carbon atoms provided that when z is a double bond then X is not O, S or NR<sup>3</sup>;

R<sup>1</sup> is hydrogen or hydroxy;

20 n is 0, 1 or 2;

Q is -CH=CH- or -C=C-; and

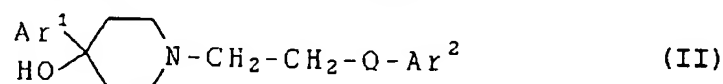
R<sup>4</sup> is hydrogen or hydroxy when z is a single bond, 25 provided that when R<sup>4</sup> is hydroxy then R<sup>2</sup> is not hydroxy or lower alkoxy. The invention also relates to a method for treating disorders responsive to the selective blockade of N-methyl-D-aspartate receptor subtypes in an animal suffering thereof comprising 30 administering in unit dosage form at least one intermediate compound represented by the formula (X).

#### DETAILED DESCRIPTION OF THE INVENTION

35 The novel 4-substituted piperidine analogs of this invention are represented by previously defined formula (I). Generally, Q is preferably -C=C-. In addition,

Ar<sup>2</sup> is preferably a pyridynyl or a phenyl group unsubstituted or substituted by halogen, amino or a lower alkyl amino group. Preferably Ar<sup>1</sup> is phenyl, more preferably phenyl substituted by a halogen group and  
 5 most preferably 4-chlorophenyl.

Preferred embodiments of the novel 4-substituted piperidine analogs of this invention are represented by formula (II-VII). In particular, a first embodiment is  
 10 represented by formula (II) as follows:

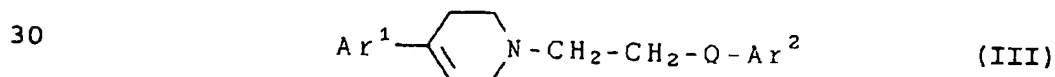


or a pharmaceutically acceptable salt thereof wherein:

15 Ar<sup>1</sup> and Ar<sup>2</sup> are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an  
 20 alkylguanidine group, a lower alkyl amino group or a lower alkoxy group; and

Q is -CH=CH- or -C≡C-, provided that when Q is -C≡C- then Ar<sup>1</sup> is aryl substituted by halogen. Preferably,  
 25 when Q is -C≡C- then Ar<sup>2</sup> is substituted by amino.

Another embodiment of the novel 4-substituted piperidines of this invention is represented by formula (III) as follows:



or a pharmaceutically acceptable salt thereof wherein;

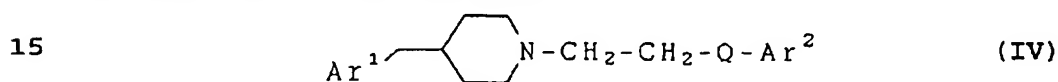
35 Ar<sup>1</sup> and Ar<sup>2</sup> are independently aryl or a heteroaryl group, either of which may be independently substituted

- 20 -

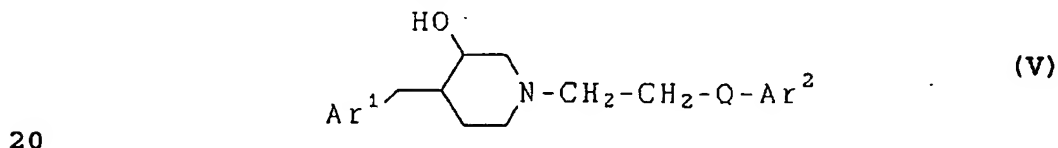
by hydrogen, hydroxy, alkyl, halogen, nitro, aryl,  
 aralkyl, amino, a halogenated alkyl group, -NHAc,  
 -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an  
 alkylguanidine group, a lower alkyl amino group or a  
 5 lower alkoxy group; and

Q is -CH=CH- or -C≡C-, provided that when Q is -C≡C-  
 then Ar<sup>1</sup> is aryl substituted by halogen. Preferably,  
 when Q is -C≡C- then Ar<sup>2</sup> is substituted by an amino or  
 10 hydroxy group.

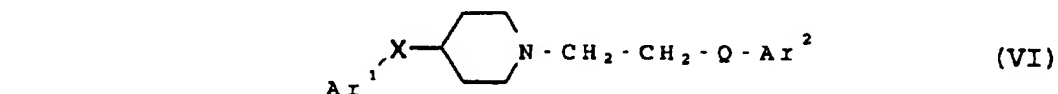
Three additional embodiments of the novel 4-substituted  
 piperidines of this invention are represented by  
 formula (IV-VI) as follows:



or a pharmaceutically acceptable salt thereof,



or a pharmaceutically acceptable salt thereof, or



or a pharmaceutically acceptable salt thereof, wherein:

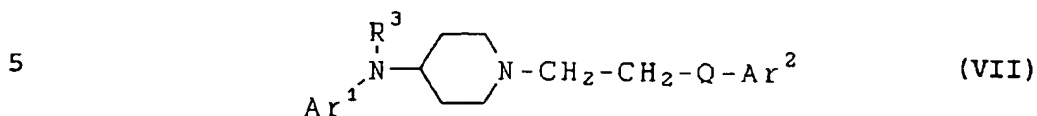
Ar<sup>1</sup> and Ar<sup>2</sup> are independently aryl or a heteroaryl  
 group, either of which may be independently substituted  
 30 by hydrogen, hydroxy, alkyl, halogen, nitro, aryl,  
 aralkyl, amino, a halogenated alkyl group, -NHAc,  
 -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an  
 alkylguanidine group, a lower alkyl amino group or a  
 lower alkoxy group; and

35

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Q is  $-\text{CH}=\text{CH}-$  or  $-\text{C}\equiv\text{C}-$ . For formula (VI) X is O or S.

Yet another embodiment of the invention is represented by the formula (VII):



or a pharmaceutically acceptable salt thereof wherein:

Ar<sup>1</sup> and Ar<sup>2</sup> are independently aryl or a heteroaryl  
 10 group, either of which may be independently substituted by hydrogen, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an alkylguanidine group, a lower alkyl amino group or a lower alkoxy group; and

15

Q is  $-\text{CH}=\text{CH}-$  or  $-\text{C}\equiv\text{C}-$ ; and

R<sup>3</sup> is hydrogen or a lower alkoxy group having 1 to 6 carbon atoms.

20

Exemplary preferred compounds of formula I include, without limitation:

\*\* 1-[4-(3-aminophenyl)-3-butynyl]-4-hydroxy-4-(4-chlorophenyl)piperidine;

25

\*\* 1-[4-(5-(2-amino)pyridinyl)-3-butynyl]-4-hydroxy-4-(4-chlorophenyl)piperidine;

\* 1-[4-(4-fluorophenyl)-3-butynyl]-4-hydroxy-4-(4-chlorophenyl)piperidine;

30

\* 1-[5-(3-aminophenyl)-4-pentynyl]-4-hydroxy-4-(4-chlorophenyl)piperidine;

35

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- \*\* 1-[4-(3-aminophenyl)-3-butynyl]-4-(4-chlorophenyl)-  
1,2,5,6-tetrahydropyridine;
- \*\* 1-[4-(5-(2-amino)pyridynyl)-3-butynyl]-4-(4-  
5 chlorophenyl)-1,2,5,6-tetrahydropyridine;
- \* 1-[4-(4-fluorophenyl)-3-butynyl]-4-(4-chlorophenyl)-  
1,2,5,6-tetrahydropyridine;
- 10 \* 1-[5-(3-aminophenyl)-4-pentynyl]-4-(4-chlorophenyl)-  
1,2,5,6-tetrahydropyridine;
- \* 4-Benzyl-1-[4-(3-aminophenyl)-3-butynyl]piperidine;
- 15 4-Benzyl-1-(4-phenyl-3-butynyl)piperidine;
- \*\* 4-(4-Chloro)benzyl-1-[4-(3-aminophenyl)-3-  
butynyl]piperidine;
- 20 \*\* 4-(4-Chloro)benzyl-1-[4-(4-hydroxyphenyl-3-  
butynyl]piperidine
- \*\* 4-(4-chloro)benzyl-1-[4-(5-(2-amino)pyridynyl)-3-  
butynyl]piperidine;
- 25 \* 1-[4-(4-fluorophenyl)-3-butynyl]-4-(3-  
trifluoromethylbenzyl)-piperidine;
- \* 4-(4-chlorobenzyl)-1-[5-(3-aminophenyl)-4-pentynyl]-  
30 piperidine;
- \* 4-Benzyl-1-[4-(3-aminophenyl)-3-butynyl]-3-  
hydroxypiperidine;
- 35 4-Benzyl-1-(4-phenyl-3-butynyl)-3-hydroxypiperidine;

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- \*\* 4-(4-Chloro)benzyl-1-[4-(3-aminophenyl)-3-butynyl]-3-hydroxypiperidine;
- \*\* 4-(4-chloro)benzyl-1-[4-(5-(2-amino)pyridynyl)-3-butynyl]-3-hydroxypiperidine;
- 5
- \* 1-[4-(4-fluorophenyl)-3-butynyl]-4-(3-trifluoromethylbenzyl)-3-hydroxy-piperidine;
- 10 \* 4-(4-chlorobenzyl)-3-hydroxy-1-[5-(3-aminophenyl)-4-pentynyl]-piperidine;
- \* 1-[4-(3-aminophenyl)-3-butynyl]-4-phenoxy-piperidine;
- 15 1-(4-phenyl-3-butynyl)-4-phenoxy-piperidine;
- \*\* 1-[4-(3-aminophenyl)-3-butynyl]-4-(4-chloro)phenoxy-piperidine;
- 20 \*\* 1-[4-(5-(2-amino)pyridynyl)-4-butynyl]-4-(4-chloro)phenoxy-piperidine;
- \* 1-[4-(4-fluorophenyl)-3-butynyl]-4-(3-trifluoromethyl)phenoxy-piperidine;
- 25 \* 1-[5-(3-aminophenyl)-4-pentynyl]-4-(4-chloro)phenoxy-piperidine;
- \* 1-[4-(3-aminophenyl)-3-butynyl]-4-(phenyl)aminopiperidine;
- 30 1-(4-phenyl-3-butynyl)-4-(phenyl)aminopiperidine;
- \*\* 1-[4-(3-aminophenyl)-3-butynyl]-4-(4-chlorophenyl)aminopiperidine;
- 35

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- \*\* 1- [4- (5- (2-amino)pyridynyl) -3-butynyl] -4- (4-chlorophenyl)aminopiperidine;
- \* 1- [4- (4-fluorophenyl) -3-butynyl] -4- (3-trifluoromethylphenyl)aminopiperidine;
- 5
- \* 4-phenyl-1- (4-phenyl-3-butynyl)piperidine;
- 4- (3- (trifluoromethyl)phenyl) -3-hydroxy-1- (4-phenyl-3-butynyl)piperidine;
- 10
- \* 1- (4- (4-aminophenyl) -3-butynyl) -4- (4-chlorophenyl) -4-hydroxypiperidine;
- 15
- N-n-butyl-N' - (3- (4- (4- (4-chlorophenyl) -4-hydroxy)piperidinyl)butynyl)phenylguanidine;
- \*\* 4-benzyl-1- (4- (3-methylphenyl) -3-butynyl)piperidine;
- 20
- \*\* 1- (4- (4-aminophenyl) -3-butynyl) -4-benzylpiperidine;
- \*\* 1- (4- (4-aminophenyl) -3-butynyl) -4- (4-chlorobenzyl)piperidine;
- 25
- \*\* 1- (4- (4-amino-3-fluorophenyl) -3-butynyl) -4- (4-chlorobenzyl)piperidine;
- N-4- (1- (4- (3-aminophenyl)butyn-3-yl)piperidinyl) -2-oxobenzimidazol;
- 30
- \*\* 1- (4- (2-aminophenyl) -3-butynyl) -4-phenylpiperidine;
- and
- \* 1- [5- (3-aminophenyl) -4-pentynyl] -4- (4-chlorophenyl)aminopiperidine;
- 35

- 25 -

4-{4-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-but-1-ynyl}-phenylamine;

5 N-{4-[4-(4-Phenoxy-piperidin-1-yl)-but-1-ynyl]-phenyl}-acetamide;

4-{4-[4-(4-Methyl-benzyl)-piperidin-1-yl]-but-1-ynyl}-phenylamine;

10 4-Benzyl-1-[4-(4-nitro-phenyl)-but-3-ynyl]-piperidine;

4-Benzyl-1-[4-(4-methoxy-phenyl)-but-3-ynyl]-piperidine;

15 4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenol;

4-Benzyl-1-[4-(4-fluoro-phenyl)-but-3-ynyl]-piperidine;

20 4-Benzyl-1-[4-(4-chloro-phenyl)-but-3-ynyl]-piperidine;

4-Benzyl-1-[4-(3-chloro-phenyl)-but-3-ynyl]-piperidine;

25 4-Benzyl-1-[4-(2,3-dichloro-phenyl)-but-3-ynyl]-piperidine;

4-Benzyl-1-[4-(3,4-dichloro-phenyl)-but-3-ynyl]-piperidine;

30 4-Benzyl-1-(4-p-tolyl-but-3-ynyl)-piperidine;

4-Benzyl-1-[4-(2,3-dimethyl-phenyl)-but-3-ynyl]-piperidine;

35 4-Benzyl-1-[4-(3,4-dimethyl-phenyl)-but-3-ynyl]-piperidine;

3-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenylamine;



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- 3 - [4 - (4-Benzyl-piperidin-1-yl) -but-1-ynyl] -benzylamine;
- N - {4 - [4 - (4-Benzyl-piperidin-1-yl) -but-1-ynyl] -phenyl} -  
acetamide;
- 5       {4 - [4 - (4-Benzyl-piperidin-1-yl) -but-1-ynyl] -phenyl} -  
methyl-amine;
- 10       {4 - [4 - (4-Benzyl-piperidin-1-yl) -but-1-ynyl] -phenyl} -  
dimethyl-amine;
- N - {4 - [4 - (4-Benzyl-piperidin-1-yl) -but-1-ynyl] -phenyl} -  
methanesulfonamide;
- 15       4 - [4 - (4-Benzyl-piperidin-1-yl) -but-1-ynyl] -benzamide;
- N - (Methylsulfonyl) -N - [4 - [4 - (phenylmethyl) -1-  
piperidiny] -1-butynyl]phenyl] -methanesulfonamide;
- 20       4 - [4 - (4-Benzyl-piperidin-1-yl) -but-1-ynyl] -  
benzenesulfonamide;
- 4 - [4 - (4-Benzyl-piperidin-1-yl) -but-1-ynyl] -N-butyl-  
benzamide;
- 25       1 - (4-Benzo[1,3]dioxol-5-yl-but-3-ynyl) -4-benzyl-  
piperidine;
- 4-Benzyl-1 - [4 - (2,3-dihydro-benzo[1,4]dioxin-6-yl) -but-  
30       3-ynyl] -piperidine;
- 4 - [3 - (4-Benzyl-piperidin-1-yl) -prop-1-ynyl] -  
phenylamine;
- 35       N - {4 - [3 - (4-Benzyl-piperidin-1-yl) -prop-1-ynyl] -phenyl} -  
methanesulfonamide;

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N-{4-[4-(4-Phenylsulfanyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-acetamide;

5 5-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-1H-indole;

4-{4-[4-(4-Methyl-benzyl)-piperidin-1-yl]-but-1-ynyl}-phenol;

10 5-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-1H-indazole;

4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-2-nitro-phenylamine;

15 4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-benzene-1,2-diamine;

5-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-1,3-dihydro-benzoimidazol-2-one;

20 N-{4-[4-(4-Phenylsulfanyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-methanesulfonamide;

4-[3-(4-Benzyl-piperidin-1-yl)-prop-1-ynyl]-benzamide;

25 4-[3-(4-Benzyl-piperidin-1-yl)-prop-1-ynyl]-benzenesulfonamide;

5-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-1H-indole-2,3-dione;

30 4-benzyl-4-hydroxy-1-(4-(3-methylphenyl)-3-butynyl)piperidine;

4-benzyl-4-hydroxy-1-(4-phenyl-3-butynyl)piperidine;

35 4-benzyl-4-hydroxy-1-(4-(4-aminophenyl)-3-butynyl)piperidine; and

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4-(4-methylbenzyl)-4-hydroxy-1-(4-(4-aminophenyl)-3-butynyl)piperidine.

Of the above-listed exemplary compounds, the more preferred compounds are designated \* and the most preferred are designated \*\*.

The invention is also directed to a method for treating disorders responsive to the selective blockade of NMDA receptor subtypes in animals suffering thereof. Particular preferred embodiments of the 4-substituted piperidine analogs for use in the method of this invention are represented by previously defined formula (IV-VII), as well as formula (II-III) wherein Q may be selected from  $-\text{CH}=\text{CH}-$  and  $-\text{C}\equiv\text{C}-$  without restriction.

Exemplary preferred compounds that may be employed in the method of this invention include, without limitation:

- \*\* 1-[4-(3-Aminophenyl)-3-butynyl]-4-hydroxy-4-(4-chlorophenyl)piperidine;
- 1-((4-Phenyl)-3-butynyl)-4-hydroxy-4-phenylpiperidine;
- \* 1-[4-(3-Aminophenyl)-3-butynyl]-4-hydroxy-4-phenylpiperidine;
- \*\* 1-[4-(5-(2-Amino)pyridinyl)-3-butynyl]-4-hydroxy-4-(4-chlorophenyl)piperidine;
- \* 1-[4-(4-Fluorophenyl)-3-butynyl]-4-hydroxy-4-(4-chlorophenyl)piperidine;
- \* 1-[5-(3-Aminophenyl)-4-pentynyl]-4-hydroxy-4-(4-chlorophenyl)piperidine;

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\*\* 1-[4-(3-Aminophenyl)-3-butynyl]-4-(4-chlorophenyl)-  
1,2,5,6-tetrahydropyridine;

1-((4-Phenyl)-3-butynyl)-4-phenyl-1,2,5,6-  
5 tetrahydropyridine;

\* 1-[4-(3-Aminophenyl)-3-butynyl]-4-phenyl-1,2,5,6-  
tetrahydropyridine;

10 \*\* 1-[4-(5-(2-Amino)pyridynyl)-3-butynyl]-4-(4-  
chlorophenyl)-1,2,5,6-tetrahydropyridine;

\* 1-[4-(4-Fluorophenyl)-3-butynyl]-4-(4-chlorophenyl)-  
1,2,5,6-tetrahydropyridine;

15

\* 1-[5-(3-Aminophenyl)-4-pentynyl]-4-(4-chlorophenyl)-  
1,2,5,6-tetrahydropyridine;

\* 4-Benzyl-1-[4-(3-aminophenyl)-3-butynyl]piperidine;

20

4-Benzyl-1-(4-phenyl-3-butynyl)piperidine;

\*\* 4-(4-Chloro)benzyl-1-[4-(3-aminophenyl)-3-  
butynyl]piperidine;

25

\*\* 4-(4-Chloro)benzyl-1-[4-(4-hydroxyphenyl)-3-  
butynyl]piperidine;

\*\* 4-(4-Chloro)benzyl-1-[4-(5-(2-amino)pyridynyl)-3-  
30 butynyl]-piperidine;

\* 1-[4-(4-Fluorophenyl)-3-butynyl]-4-(3-  
trifluoromethylbenzyl)-piperidine;

35 \* 4-(4-Chlorobenzyl)-1-[5-(3-aminophenyl)-4-pentynyl]-  
piperidine;

- 30 -

- \*4-Benzyl-1-[4-(3-aminophenyl)-3-butynyl]-3-hydroxypiperidine;
- 5 4-Benzyl-1-(4-phenyl-3-butynyl)-3-hydroxypiperidine;
- \*\* 4-(4-Chloro)benzyl-1-[4-(3-aminophenyl)-3-butynyl]-3-hydroxypiperidine;
- 10 \*\* 4-(4-chloro)benzyl-1-[4-(5-(2-amino)pyridynyl)-3-butynyl]-3-hydroxypiperidine;
- \* 1-[4-(4-Fluorophenyl)-3-butynyl]-4-(3-trifluoromethylbenzyl)-3-hydroxy-piperidine;
- 15 \* 4-(4-Chlorobenzyl)-3-hydroxy-1-[5-(3-aminophenyl)-4-pentynyl]-piperidine;
- \* 1-[4-(3-Aminophenyl)-3-butynyl]-4-phenoxy-piperidine;
- 20 1-(4-Phenyl-3-butynyl)-4-phenoxy-piperidine;
- \*\* 1-[4-(3-Aminophenyl)-3-butynyl]-4-(4-chloro)phenoxy-piperidine;
- 25 \*\* 1-[4-(5-(2-Amino)pyridynyl)-4-butynyl]-4-(4-chloro)phenoxy-piperidine;
- \* 1-[4-(4-Fluorophenyl)-3-butynyl]-4-(3-trifluoromethyl)phenoxy-piperidine;
- 30 \* 1-[5-(3-Aminophenyl)-4-pentynyl]-4-(4-chloro)phenoxy-piperidine;
- \* 1-[4-(3-Aminophenyl)-3-butynyl]-4-(phenyl)aminopiperidine;
- 35 1-(4-Phenyl-3-butynyl)-4-(phenyl)aminopiperidine;

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- \*\* 1-[4-(3-Aminophenyl)-3-butynyl]-4-(4-chlorophenyl)aminopiperidine;
- \*\* 1-[4-(5-(2-Amino)pyridynyl)-3-butynyl]-4-(4-chlorophenyl)aminopiperidine;
- 5
- \* 1-[4-(4-Fluorophenyl)-3-butynyl]-4-(3-trifluoromethylphenyl)aminopiperidine;
- 10
- \* 4-Phenyl-1-(4-phenyl-3-butynyl)piperidine;
- 4-(3-(Trifluoromethyl)phenyl)-3-hydroxy-1-(4-phenyl-3-butynyl)piperidine;
- 15
- \* 1-(4-(4-Aminophenyl)-3-butynyl)-4-(4-chlorophenyl)-4-hydroxypiperidine;
- N-n-Butyl-N'-(3-(4-(4-(4-chlorophenyl)-4-hydroxy)piperidinyl)butynyl)phenylguanidine;
- 20
- \*\* 4-Benzyl-1-(4-(3-methylphenyl)-3-butynyl)piperidine;
- \*\* 1-(4-(4-Aminophenyl)-3-butynyl)-4-benzylpiperidine;
- 25
- \*\* 4-Benzyl-4-hydroxy-1-(4-phenyl-3-butynyl)piperidine;
- \* 4-Benzyl-4-hydroxy-1-(4-(3-methylphenyl)-3-butynyl)piperidine;
- 30
- \*\* 1-(4-(4-Aminophenyl)-3-butynyl)-4-benzyl-4-hydroxypiperidine;
- \*\* 1-(4-(4-Aminophenyl)-3-butynyl)-4-(4-chlorobenzyl)piperidine;
- 35
- \*\* 1-(4-(4-Amino-3-fluorophenyl)-3-butynyl)-4-(4-chlorobenzyl)piperidine;

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N-4-(1-(4-(3-Aminophenyl)butyn-3-yl)piperidinyl)-2-oxobenzimidazol;

5       \*\* 1-(4-(2-Aminophenyl)-3-butynyl)-4-phenylpiperidine;

\* 1-[5-(3-Aminophenyl)-4-pentynyl]-4-(4-chlorophenyl)aminopiperidine;

10       4-{4-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-but-1-ynyl}-phenylamine;

N-{4-[4-(4-Phenoxy-piperidin-1-yl)-but-1-ynyl]-phenyl}-acetamide;

15       4-{4-[4-(4-Methyl-benzyl)-piperidin-1-yl]-but-1-ynyl}-phenylamine;

4-Benzyl-1-[4-(4-nitro-phenyl)-but-3-ynyl]-piperidine;

20       4-Benzyl-1-[4-(4-methoxy-phenyl)-but-3-ynyl]-piperidine;

4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenol;

25       4-Benzyl-1-[4-(4-fluoro-phenyl)-but-3-ynyl]-piperidine;

4-Benzyl-1-[4-(4-chloro-phenyl)-but-3-ynyl]-piperidine;

30       4-Benzyl-1-[4-(3-chloro-phenyl)-but-3-ynyl]-piperidine;

4-Benzyl-1-[4-(2,3-dichloro-phenyl)-but-3-ynyl]-piperidine;

35       4-Benzyl-1-[4-(3,4-dichloro-phenyl)-but-3-ynyl]-piperidine;

4-Benzyl-1-(4-p-tolyl-but-3-ynyl)-piperidine;

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4-Benzyl-1-[4-(2,3-dimethyl-phenyl)-but-3-ynyl]-  
piperidine;

4-Benzyl-1-[4-(3,4-dimethyl-phenyl)-but-3-ynyl]-  
5 piperidine;

3-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenylamine;

3-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-benzylamine;  
10

N-{4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-  
acetamide;

{4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-  
15 methyl-amine;

{4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-  
dimethyl-amine;

20 N-{4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-  
methanesulfonamide;

4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-benzamide;

25 N-(Methylsulfonyl)-N-[4-[4-(phenylmethyl)-1-  
piperidinyl]-1-butynyl]phenyl]-methanesulfonamide;

4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-  
benzenesulfonamide;

30 4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-N-butyl-  
benzamide;

1-(4-Benzo[1,3]dioxol-5-yl-but-3-ynyl)-4-benzyl-  
35 piperidine;



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- 4-Benzyl-1-[4-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-but-3-ynyl]-piperidine;
- 4-[3-(4-Benzyl-piperidin-1-yl)-prop-1-ynyl]-  
5 phenylamine;
- N-{4-[3-(4-Benzyl-piperidin-1-yl)-prop-1-ynyl]-phenyl}-methanesulfonamide;
- 10 N-{4-[4-(4-Phenylsulfanyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-acetamide;
- 5-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-1H-indole;
- 15 4-[4-[4-(4-Methyl-benzyl)-piperidin-1-yl]-but-1-ynyl]-phenol;
- 5-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-1H-indazole;
- 20 4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-2-nitrophenylamine;
- 4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-benzene-1,2-diamine;
- 25 5-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-1,3-dihydrobenzoimidazol-2-one;
- N-{4-[4-(4-Phenylsulfanyl-piperidin-1-yl)-but-1-ynyl]-  
30 phenyl}-methanesulfonamide;
- 4-[3-(4-Benzyl-piperidin-1-yl)-prop-1-ynyl]-benzamide;
- 4-[3-(4-Benzyl-piperidin-1-yl)-prop-1-ynyl]-  
35 benzenesulfonamide;

- 35 -

5- [4- (4-Benzyl-piperidin-1-yl) -but-1-ynyl] -1H-indole-  
2,3-dione;

4-benzyl-4-hydroxy-1-4- (3-methylphenyl) -3-  
5 butynyl)piperidine;

4-benzyl-4-hydroxy-1- (4-phenyl-3-butynyl)piperidine;

4-benzyl-4-hydroxy-1- (4- (4-aminophenyl) -3-  
10 butynyl)piperidine; and

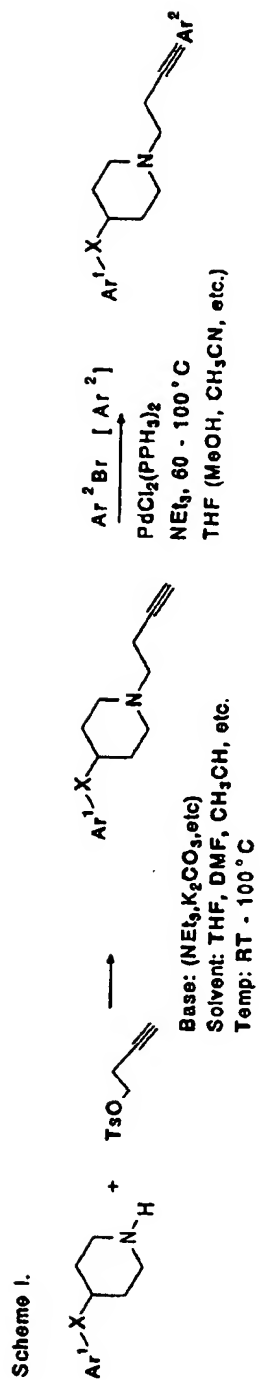
4- (4-methylbenzyl) -4-hydroxy-1- (4- (4-aminophenyl) -3-  
butynyl)piperidine.

15 Of the above-listed exemplary compounds, the more  
preferred compounds for use in the method of this  
invention are designated \* and the most preferred are  
designated \*\*.

20 The compounds of this invention may be prepared using  
methods well known to those skilled in the art such as  
disclosed in U.S. Patent No. 5,273,977, the disclosure  
of which is incorporated by reference herein, or by the  
novel methods of this invention. Exemplary reaction  
25 schemes I and II illustrate preparations of the  
compounds of this invention having alkyne  
functionality. The starting materials employed in  
Schemes I and II are readily available or can be  
prepared by known methods.

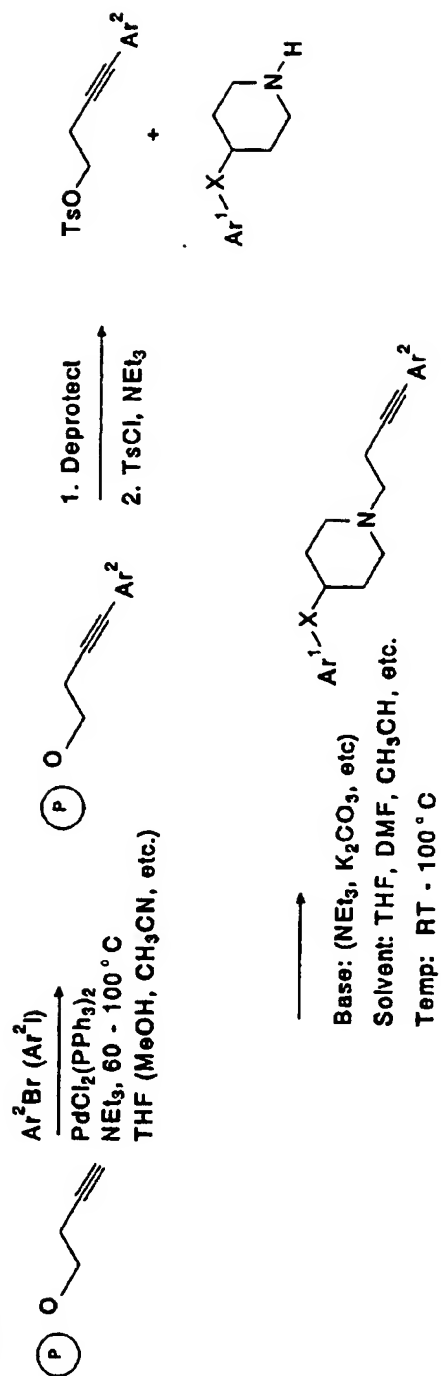
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Scheme II.



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The methods set forth herein, may also be employed to prepare novel intermediates of this invention. The preferred novel intermediates include:

- 5 1-(3-Butynyl)-4-hydroxy-4-phenylpiperidine;
- 1-(3-Butynyl)-4-hydroxy-4-((4-chloro)phenyl)piperidine;
- 1-(3-Butynyl)-4-hydroxy-4-((3-
- 10 trifluoromethyl)phenyl)piperidine;
- 4-Hydroxy-4-phenyl-1-(2-propynyl)piperidine;
- 4-Hydroxy-1-(4-pentynyl)-4-phenylpiperidine;
- 15 1-(3-Butynyl)-4-(4-chloro)phenyl-1,2,5,6-
- tetrahydropyridine;
- 1-(3-Butynyl)-4-(4-trifluoromethyl)phenyl-1,2,5,6-
- 20 tetrahydropyridine;
- 4-(4-Chloro)phenyl-1-(2-propynyl)-1,2,5,6-
- tetrahydropyridine;
- 25 4-(4-Chloro)phenyl-1-(4-pentynyl)-1,2,5,6-
- tetrahydropyridine;
- 4-Benzyl-1-(3-butynyl)piperidine;
- 30 4-(4-Chloro)benzyl-1-(3-butynyl)piperidine;
- 4-(3-Trifluoromethyl)benzyl-1-(3-butynyl)piperidine;
- 4-(4-Chloro)benzyl-1-(2-propynyl)piperidine;
- 35 4-(4-Chloro)benzyl-1-(4-pentynyl)piperidine;

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- 4-Benzyl-1-(3-butynyl)-3-hydroxy-piperidine;
- 4-(4-Chloro)benzyl-1-(3-butynyl)-3-hydroxy-piperidine;
- 5 4-(3-Trifluoromethyl)benzyl-1-(3-butynyl)-3-hydroxy-piperidine;
- 4-(4-Chloro)benzyl-3-hydroxy-1-(2-propynyl)piperidine;
- 10 4-(4-Chloro)benzyl-3-hydroxy-1-(4-pentynyl)piperidine;
- 1-(3-Butynyl)-4-phenoxy-piperidine;
- 1-(3-Butynyl)-4-(4-chloro)phenoxy-piperidine;
- 15 1-(3-Butynyl)-4-(3-trifluoromethyl)phenoxy-piperidine;
- 4-(4-Chloro)phenoxy-1-(2-propynyl)piperidine;
- 20 1-(4-Pentynyl)-4-(4-chloro)phenoxy-piperidine;
- 1-(3-Butynyl)-4-(phenyl)aminopiperidine;
- 1-(3-Butynyl)-4-((4-chloro)phenyl)aminopiperidine;
- 25 1-(3-Butynyl)-4-((3-trifluoromethyl)phenyl)aminopiperidine;
- 4-((4-Chloro)phenyl)amino-1-(2-propynyl)piperidine;
- 30 1-(But-3-ynyl)-4-(4-chlorobenzyl)piperidine;
- 4-Benzyl-1-(but-3-yn-1-yl)-4-hydroxypiperidine;
- 35 4-(4-Methylbenzyl)-4-hydroxy-1-(but-3-yn-1-yl)piperidine; and

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1-(4-Pentynyl)4-((4-chloro)phenyl)aminopiperidine.

The compounds of the present invention are useful in treating or preventing neuronal loss, neurodegenerative diseases and chronic pain. They are also useful as anticonvulsants and for inducing anesthesia, as well as for treating epilepsy and psychosis. The therapeutic and side effect profiles of subtype-selective NMDA receptor antagonists and agonists should be markedly different from the more non-subtype-selective NMDA receptor inhibitors. The subtype-selective analogs of the present invention are expected to exhibit little or no untoward side effects caused by non-specific binding with other receptors, particularly, the PCP and glutamate bindings sites associated with the NMDA receptor. In addition, selectivity for different NMDA receptor subtypes will reduce side effects such as sedation that are common to non-subtype-selective NMDA receptor antagonists. The compounds of the present invention are effective in treating or preventing the adverse consequences of the hyperactivity of excitatory amino acids, e.g. those which are involved in the NMDA receptor system, by preventing the ligand-gated cation channels from opening and allowing excessive influx of  $\text{Ca}^{++}$  into neurons, as occurs during ischemia.

Neurodegenerative diseases which may be treated with the compounds of the present invention include those selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease and Down's syndrome.

The compounds of the present invention find particular utility in the treatment or prevention of neuronal loss associated with multiple strokes which give rise to dementia. After a patient has been diagnosed as suffering from a stroke, the compounds of the present

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invention may be administered to ameliorate the immediate ischemia and prevent further neuronal damage that may occur from recurrent strokes.

- 5 Moreover, the compounds of the present invention are able to cross the blood/brain barrier which makes them particularly useful for treating or preventing conditions involving the central nervous system.
- 10 The compounds of the invention find particular utility in treating or preventing the adverse neurological consequences of surgery. For example, coronary bypass surgery requires the use of heart-lung machines which tend to introduce air bubbles into the circulatory
- 15 system which may lodge in the brain. The presence of such air bubbles robs neuronal tissue of oxygen, resulting in anoxia and ischemia. Pre- or post-surgical administration of the compounds of the present invention will treat or prevent the resulting ischemia.
- 20 In a preferred embodiment, the compounds of the invention are administered to patients undergoing cardiopulmonary bypass surgery or carotid endarterectomy surgery.
- 25 The compounds of the present invention also find utility in treating or preventing chronic pain. Such chronic pain may be the result of surgery, trauma, headache, arthritis, pain from terminal cancer or degenerative diseases. The compounds of the present
- 30 invention also find particular utility in the treatment of phantom pain that results from amputation of an extremity. In addition to treatment of pain, the compounds of the invention are also expected to be useful in inducing anesthesia, either general or local
- 35 anesthesia, for example, during surgery.



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The selective NMDA receptor subtype antagonists, agonists and modulators may be tested for in vivo anticonvulsant activity after intraperitoneal or intravenous injection using a number of anticonvulsant tests in mice (audiogenic seizure model in DBA-2 mice, pentylenetetrazol-induced seizures in mice, maximum electroshock seizure test (MES) or NMDA-induced death). The compounds may also be tested in drug discrimination tests in rats trained to discriminate PCP from saline.

It is expected that most of the compounds of the present invention will not generalize to PCP at any dose. In addition, it is also expected that none of the compounds will produce a behavioral excitation in locomotor activity tests in the rodent. It is expected that such results will suggest that the selective NMDA receptor subtype antagonists and agonists of the present invention do not show the PCP-like behavioral side effects that are common to NMDA channel blockers such as MK-801 and PCP, or to competitive NMDA antagonists such as CGS 19755.

The subtype-selective NMDA receptor antagonists and agonists are also expected to show potent activity in vivo after intraperitoneal or intravenous injection suggesting that these compounds can penetrate the blood/brain barrier.

Elevated levels of glutamate has been associated with glaucoma. In addition, it has been disclosed that glaucoma management, particularly protection of retinal ganglion cells, can be achieved by administering to a patient a compound capable of reducing glutamate-induced excitotoxicity in a concentration effective to reduce the excitotoxicity. See WO94/13275. Thus, the compounds of the present invention, which are expected to cross the blood-retina barrier, are also expected to be useful in the treatment of glaucoma. Preferably,

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the invention is directed to the treatment of patients which have primary open-angle glaucoma, chronic closed-angle glaucoma, pseudo exfoliation, or other types of glaucoma or ocular hypertension. Preferably, the  
5 compound is administered over an extended period (e.g. at least six months and preferably at least one year), regardless of the changes in the patient's intraocular pressure over the period of administration. The compounds of the present invention are also useful in  
10 treating CMV retinitis, particularly in combination with antiviral agents. CMV afflicts the ganglion cell layer which may result in higher levels of glutamate. Thus, NMDA receptor antagonists could block retinitis by blocking the toxicity effect of high levels of  
15 glutamate.

Aminoglycoside antibiotics have been used successfully in the treatment of serious Gram-negative bacterial infections. However, prolonged treatment with these  
20 antibiotics will result in the destruction of sensory hearing cells of the inner ear and consequently, induce permanent loss of hearing. A recent study of Basile, et al. (Nature Medicine, 2: 1338-1344, 1996) indicated that aminoglycosides produce a polyamine-like  
25 enhancement of glutamate excitotoxicity through their interaction with the NMDA receptor. Thus, compounds of the present invention with NMDA receptor antagonist activity will be useful in preventing aminoglycoside antibiotics-induced hearing loss by antagonizing their  
30 interaction with the receptor.

The compounds of the present invention are useful in treating headaches, in particular, migraine headaches. During migraine attack, a sensory disturbance with  
35 unique changes of brain blood flow will result in the development of characteristic migraine auras. Since this unique phenomena has been replicated in animal

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experiments with cortical-spreading depression (CSD) of  
Leaó, A.A.P.J., Neurophysiol. 7:359-390 (1944), CSD is  
considered an important phenomena in the  
pathophysiology of migraine with aura (Tepley et al.,  
5 In: Biomagnetism, eds. S. Williamson, L. Kaufmann, pp.  
327-330, Plenum Press, New York (1990)). The CSD is  
associated with the propagation (2-6mm/s) of transient  
changes in electrical activity which relate to the  
failure of ion homeostasis in the brain, efflux of  
10 excitatory amino acids from the neurons and increased  
energy metabolism (Lauritzen, M., Acta Neurol. Scand.  
76 (Suppl. 113):4-40 (1987)). It has been demonstrated  
that the initiation of CSD in a variety of animals,  
including humans, involved the release of glutamate and  
15 could be triggered by NMDA (Curtis et al., Nature  
191:1010-1011 (1961); and Lauritzen et al., Brain Res.  
475:317-327 (1988)). Subtype selective NMDA  
antagonists will be therapeutically useful for migraine  
headache because of their expected low side effects,  
20 their ability to cross the blood brain barrier and  
their systemic bioavailability.

Bladder activity is controlled by parasympathetic  
preganglionic neurons in the sacral spinal cord  
25 (DeGroat et al., J. Auton. Nerv. Sys. 3:135-160(1981)).  
In humans, it has been shown that the highest density  
of NMDA receptors in the spinal cord are located at the  
sacral level, including those areas that putatively  
contain bladder parasympathetic preganglionic neurons  
30 (Shaw et al., Brain Research 539:164-168 (1991)).  
Because NMDA receptors are excitatory in nature,  
pharmacological blockade of these receptors would  
suppress bladder activity. It has been shown that the  
noncompetitive NMDA receptor antagonist MK801 increased  
35 the frequency of micturition in rat (Vera and  
Nadelhaft, Neuroscience Letters 134:135-138(1991)). In  
addition, competitive NMDA receptor antagonists have

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also been shown to produce a dose-dependent inhibition of bladder and of urethral sphincter activity (US Patent 5,192,751). Thus, it is anticipated that subtype-selective NMDA receptor antagonists will be effective in the treatment of urinary incontinence mediated by their modulation on the receptor channel activity.

Non-competitive NMDA receptor antagonist MK801 has been shown to be effective in a variety of animal models of anxiety which are highly predictive of human anxiety (Clineschmidt, B.V. et al., Drug Dev. Res. 2:147-163 (1982)). In addition, NMDA receptor glycine site antagonists are shown to be effective in the rat potentiated startle test (Anthony, E.W., Eur. J. Pharmacol. 250:317-324 (1993)) as well as several other animal anxiolytic models (Winslow, J. et al, Eur. J. Pharmacol. 190:11-22 (1990); Dunn, R. et al., Eur. J. Pharmacol. 214:207-214 (1992); and Kehne, J.H. et al, Eur. J. Pharmacol. 193:282-292 (1981)).

Glycine site antagonists, (+) HA-966 and 5,7-dichlorokynurenic acid were found to selectively antagonize d-amphetamine induced stimulation when injected into rat nucleus accumbens but not in striatum (Hutson, P.H. et al., Br. J. Pharmacol. 103:2037-2044 (1991)). Interestingly, (+) HA-966 was also found to block PCP and MK801-induced behavioral arousal (Bristow, L.J. et al., Br. J. Pharmacol. 108:1156-1163 (1993)). These findings suggest that a potential use of NMDA receptor channel modulators, but not channel blockers, as atypical neuroleptics.

It has been shown that in an animal model of Parkinson's disease - MPP<sup>+</sup> or methamphetamine-induced damage to dopaminergic neurons - can be inhibited by NMDA receptor antagonists (Rojas et al., Drug Dev. Res.

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29:222-226 (1993); and Sonsalla et al, Science 243:398-400 (1989)). In addition, NMDA receptor antagonists have been shown to inhibit haloperidol-induced catalepsy (Schmidt, W.J. et al., Amino Acids 1:225-237 (1991)), increase activity in rodents depleted of monoamines (Carlsson et al., Trends Neurosci. 13:272-276 (1990)) and increase ipsilateral rotation after unilateral substantia nigra lesion in rats (Snell, L.D. et al., J. Pharmacol. Exp. Ther. 235:50-57 (1985)).

10 These are also experimental animal models of Parkinson's disease. In animal studies, the antiparkinsonian agent amantadine and memantine showed antiparkinsonian-like activity in animals at plasma levels leading to NMDA receptor antagonism (Danysz, W. et al., J. Neural Trans. 7:155-166, (1994)). Thus, it is possible that these antiparkinsonian agents act therapeutically through antagonism of an NMDA receptor. Therefore, the balance of NMDA receptor activity maybe important for the regulation of extrapyramidal function

20 relating to the appearance of parkinsonian symptoms.

It is well known to use opiates, e.g., morphine, in the medical field to alleviate pain. (As used herein, the term "opiates" is intended to mean any preparation or derivative of opium, especially the alkaloids naturally contained therein, of which there are about twenty, e.g., morphine, noscapine, codeine, papaverine, and thebaine, and their derivatives.) Unfortunately, with continued use, the body builds up a tolerance for the opiate, and, thus, for continued relief, the patient must be subjected to progressively larger doses. Tolerance develops after both acute and chronic morphine administration (Kornetsky et al., Science 162:1011-1012 (1968); Way et al., J. Pharmacol. Exp Ther. 167:1-8 (1969); Huidobro et al., J. Pharmacol. Exp Ther. 198:318-329 (1976); Lutfy et al., J. Pharmacol. Exp Ther. 256:575-580 (1991)). This, in

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itself, can be detrimental to the patient's health. Furthermore, a time can come when the tolerance is substantially complete and the pain killing properties of the drug are no longer effective. Additionally, administration of higher doses of morphine may lead to respiratory depression, causing the patient to stop breathing. Seeking alternative drugs to produce analgesia without development of tolerance or as an adjunct therapy to block tolerance without interference with analgesia is an active area of research.

Recent studies have suggested a modulatory role for the NMDA receptor in morphine tolerance. (Trujillo et al., Science 251:85-87 (1991); Marek et al., Brain Res. 547:77-81 (1991); Tiseo et al., J. Pharmacol. Exp Ther. 264:1090-1096 (1993); Lutfy et al., Brain Res. 616:83-88 (1993); Herman et al., Neuropsychopharmacology 12:269-294 (1995).) Further, it has been reported that NMDA receptor antagonists are useful for inhibiting opioid tolerance and some of the symptoms of opioid withdrawal. Thus, the present invention is also directed to the administration of the compounds described herein to inhibit opiate tolerance and to treat or ameliorate the symptoms of opiate withdrawal by blocking the glycine co-agonist site associated with the NMDA receptor.

Thus, the present invention is directed to compounds having high affinity to a particular NMDA receptor subunit (subtype) and low affinity to other sites such as dopamine and other catecholamine receptors. According to the present invention, those compounds having high binding to a particular NMDA subunit exhibit an  $IC_{50}$  of about 100  $\mu M$  or less in an NMDA subunit binding assay (see Table 1). Preferably, the compounds of the present invention exhibit a selective subunit  $IC_{50}$  of 10  $\mu M$  or less. More preferably, the

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compounds of the present invention exhibit a selective subunit  $IC_{50}$  of about  $1.0 \mu M$  or less, more preferably about  $0.1 \mu M$  or less.

- 5 Compositions within the scope of this invention include all compositions wherein the compounds of the present invention are contained in an amount which is effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of  
10 effective amounts of each component is within the skill of the art. Typically, the compounds may be administered to mammals, e.g. humans, orally at a dose of  $0.0025$  to  $50 \text{ mg/kg}$ , or an equivalent amount of the pharmaceutically acceptable salt thereof, per day of  
15 the body weight of the mammal being treated for anxiety disorders, e.g., generalized anxiety disorder, phobic disorders, obsessional compulsive disorder, panic disorder and post traumatic stress disorders or for schizophrenia or other psychoses. Preferably, about  
20  $0.01$  to about  $10 \text{ mg/kg}$  is orally administered to treat or prevent such disorders. For intramuscular injection, the dose is generally about one-half of the oral dose. For example, for treatment or prevention of anxiety, a suitable intramuscular dose would be about  
25  $0.0025$  to about  $15 \text{ mg/kg}$ , and most preferably, from about  $0.01$  to about  $10 \text{ mg/kg}$ .

- In the method of treatment or prevention of neuronal loss in ischemia, brain and spinal cord trauma,  
30 hypoxia, hypoglycemia, and surgery, to treat or prevent glaucoma or urinary incontinence, as well as for the treatment of Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease and Down's Syndrome, or in a method of treating a  
35 disease in which the pathophysiology of the disorder involves hyperactivity of the excitatory amino acids or NMDA receptor-ion channel related neurotoxicity, the

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pharmaceutical compositions of the invention may comprise the compounds of the present invention at a unit dose level of about 0.01 to about 50 mg/kg of body weight, or an equivalent amount of the pharmaceutically acceptable salt thereof, on a regimen of 1-4 times per day. When used to treat chronic pain, migraine headache, to induce anesthesia, to treat or prevent opiate tolerance or to treat opiate withdrawal, the compounds of the invention may be administered at a unit dosage level of from about 0.01 to about 50 mg/kg of body weight, or an equivalent amount of the pharmaceutically acceptable salt thereof, on a regimen of 1-4 times per day. Of course, it is understood that the exact treatment level will depend upon the case history of the animal, e.g., human being, that is treated. The precise treatment level can be determined by one of ordinary skill in the art without undue experimentation.

The unit oral dose may comprise from about 0.01 to about 50 mg, preferably about 0.1 to about 10 mg of the compound. The unit dose may be administered one or more times daily as one or more tablets each containing from about 0.1 to about 10, conveniently about 0.25 to 50 mg of the compound or its solvates.

In addition to administering the compound as a raw chemical, the compounds of the invention may be administered as part of a pharmaceutical preparation containing suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the compounds into preparations which can be used pharmaceutically. Preferably, the preparations, particularly those preparations which can be administered orally and which can be used for the preferred type of administration, such as tablets, dragees, and capsules, and also



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preparations which can be administered rectally, such as suppositories, as well as suitable solutions for administration by injection or orally, contain from about 0.01 to 99 percent, preferably from about 0.25 to 75 percent of active compound(s), together with the excipient.

Also included within the scope of the present invention are the non-toxic pharmaceutically acceptable salts of the compounds of the present invention. Acid addition salts are formed by mixing a solution of the particular subtype-selective NMDA receptor antagonist or agonist of the present invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid, oxalic acid, and the like.

The pharmaceutical compositions of the invention may be administered to any animal which may experience the beneficial effects of the compounds of the invention. Foremost among such animals are mammals, e.g., humans, although the invention is not intended to be so limited.

The pharmaceutical compositions of the present invention may be administered by any means that achieve their intended purpose. For example, administration may be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal routes. Alternatively, or concurrently, administration may be by the oral route. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

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The pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers such as saccharides, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as binders such as starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethylstarch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries include, without limitation, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose

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preparations such as acetyl-cellulose phthalate or hydroxypropymethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in  
5 order to characterize combinations of active compound doses.

Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as  
10 well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants  
15 such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.

20 Possible pharmaceutical preparations which can be used rectally include, for example, suppositories, which consist of a combination of one or more of the active compounds with a suppository base. Suitable  
25 suppository bases are, for example, natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the active compounds with a base. Possible base materials  
30 include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds in  
35 water-soluble form, for example, water-soluble salts and alkaline solutions. In addition, suspensions of the active compounds as appropriate oily injection

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suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400 (the compounds are soluble in PEG-400). Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

The characterization of NMDA subunit binding sites in vitro has been difficult because of the lack of selective drug ligands. Thus, the compounds of the present invention may be used to characterize the NMDA subunits and their distribution. Particularly preferred selective NMDA receptor subtype antagonists and agonists of the present invention which may be used for this purpose are isotopically radiolabelled derivatives, e.g., where one or more of the atoms are replaced with  $^3\text{H}$ ,  $^{12}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ , or  $^{18}\text{F}$ .

#### Electrophysiological Assays at NMDA receptor subunits

Preparation of RNA. cDNA clones encoding the NR1A, NR2A, NR2B, NR2C and NR2D rat NMDA receptor subtypes were provided by Dr. P.H. Seeburg (see, Moriyoshi et al., Nature (Lond.) 354:31-37 (1991); Kutsuwada et al., Nature (Lond.) 358:36-41 (1992) Monyer et al., Science (Washington, D.C.) 256:1217-1221 (1992); Ikeda et al., FEBS Lett. 313:34-38 (1992); Ishii et al., J. Biol. Chem. 268:2836-2843 (1993) for details of these clones or their mouse homologs). The clones were transformed into appropriate host bacteria and plasmid preparations were made with conventional DNA purification techniques. A sample of each clone was linearized by restriction enzyme digestion and cRNA was synthesized

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with T3 RNA polymerase. The cRNA was diluted to 400 ng/ $\mu$ l and stored in 1  $\mu$ l aliquots at -80°C until injection.

- 5 The *Xenopus* oocyte expression system. Mature female *Xenopus laevis* were anaesthetized (20-40 min) using 0.15% 3-aminobenzoic acid ethyl ester (MS-222) and 2-4 ovarian lobes were surgically removed. Oocytes at developmental stages IV-VI (Dumont, J.N., J. Morphol.  
10 136:153-180 (1972)), were dissected from the ovary still surrounded by enveloping ovarian tissues. Follicle-enclosed oocytes were micro-injected with 1:1 mixtures of cRNA:NR1A + NR2A, 2B, 2C or 2D; injecting ~2, 5, or 20 ng of RNA encoding each receptor subunit.  
15 NR1A encoding cRNA was injected alone at ~20 ng. Oocytes were stored in Barth's medium containing (in mM): NaCl, 88; KCl, 1; CaCl<sub>2</sub>, 0.41; Ca(NO<sub>3</sub>)<sub>2</sub>, 0.33; MgSO<sub>4</sub>, 0.82 NaHCO<sub>3</sub>, 2.4; HEPES 5, pH 7.4, with 0.1 mg/ml gentamicin sulphate. While oocytes were still  
20 surrounded by enveloping ovarian tissues the Barth's medium was supplemented with 0.1% bovine serum. Oocytes were defolliculated 1-2 days following injections by treatment with collagenase (0.5 mg/ml Sigma Type I for 0.5-1 hr) (Miledi and Woodward, J. Physiol. (Lond.) 416:601-621 (1989)) and subsequently  
25 stored in serum-free medium.

- Electrical recordings were made using a conventional two-electrode voltage clamp (Dagan TEV-200) over  
30 periods ranging between 3-21 days following injection. (Woodward et al., Mol. Pharmacol. 41: 89-103 (1992)). Oocytes were placed in a 0.1 ml recording chamber continuously perfused (5-15 ml min<sup>-1</sup>) with frog Ringer's solution containing (in mM): NaCl, 115; KCl, 2; CaCl<sub>2</sub>,  
35 1.8; HEPES, 5; pH 7.4. Drugs were applied by bath perfusion. Using oocytes expressing different subunit combinations of NMDA receptor, NMDA currents were

- 55 -

activated by co-application of glutamate (100  $\mu$ M) and glycine (1-100  $\mu$ M). Inhibitory potency of the novel antagonists was assessed on responses elicited by fixed concentrations of glutamate and glycine, by measuring  
5 reductions in current induced by progressively increasing concentrations of antagonist. Concentration-inhibition curves were fit with equation 1.

10 
$$I/I_{\text{control}} = 1/(1 + ([\text{antagonist}]/10^{-\text{pIC}_{50}})^n) \quad \text{Eq. 1}$$

in which  $I_{\text{control}}$  is the current evoked by agonists alone,  $\text{pIC}_{50} = -\log \text{IC}_{50}$ ,  $\text{IC}_{50}$  is the concentration of antagonist that produces half maximal inhibition, and n is the  
15 slope factor. (De Lean et al., Am. J. Physiol. 235:E97-102 (1978)). For incomplete curves analysis by fitting was unreliable and  $\text{IC}_{50}$  values were calculated by simple regression over linear portions of the curves (Origin: Microcal Software).

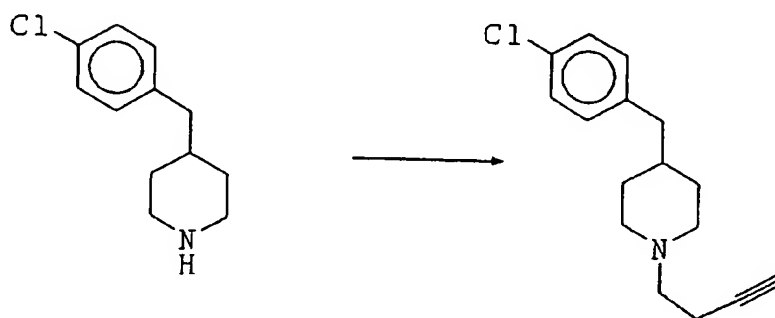
20 Maximal Electroshock-induced Seizures. Seizures were induced by application of current (50 mA, 60 pulses/sec, 0.8 sec pulse width, 1 sec duration, d.c.) through saline-coated corneal electrodes using a Ugo  
25 Basile ECT device (Model 7801). Mice were restrained by gripping the loose skin on their dorsal surface, electrodes were held lightly against the two cornea, then current was applied and mice were observed for a period of up to 30 sec for the occurrence of a tonic  
30 hindlimb extensor response. A tonic seizure was defined as a hindlimb extension in excess of 90 degrees from the plane of the body. Results were treated in a quantal manner.

35 The examples which follow are intended as an illustration of certain preferred embodiments of the

invention, and no limitation of the invention is implied.

Example 1

5 1-(3-Butynyl)-4-(4-chlorophenyl)piperidine

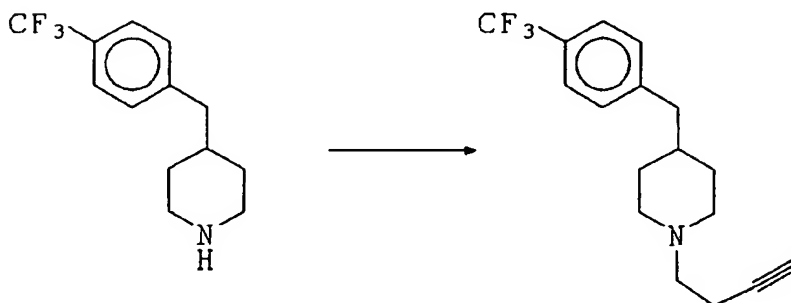


- 10 A suspension of  $\text{NaHCO}_3$  (4 g) and 4-[(4-chlorophenyl)methyl]piperidine (18 mmol) in dimethylformamide (DMF) (25 mL) is stirred under a  $\text{N}_2$  atm at  $0^\circ\text{C}$ , and treated dropwise with 3-butynyltosylate (20 mmol) as a solution in DMF (50 mL). The reaction
- 15 mixture is heated at  $80^\circ\text{C}$  and stirred an additional 18 hours. After cooling the reaction mixture is stirred vigorously with the addition of water (200 mL), and then extracted with ethyl acetate. The organic layer is dried over magnesium sulfate, filtered and
- 20 evaporated. The residue is purified by silica gel column chromatography (100:1  $\text{CH}_2\text{Cl}_2$ :MeOH) to give 1-(3-butynyl)-4-(4-chlorophenyl)piperidine.

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## Example 2

1-(3-Butynyl)-4-[(4-trifluoromethylphenyl)methyl]piperidine



5

A mixture of 4-[(4-trifluoromethylphenyl)methyl]piperidine (30 mmol),  $K_2CO_3$  (4.5 g) and 3-butynyltosylate (39 mmol) in acetonitrile (150 mL) is heated to reflux for 8 hr. After cooling, the acetonitrile is removed on a rotary evaporator and the residue partitioned between dichloromethane and water. The combined organic solution is dried over sodium sulfate, filtered and evaporated. The product is purified by silica gel column chromatography.

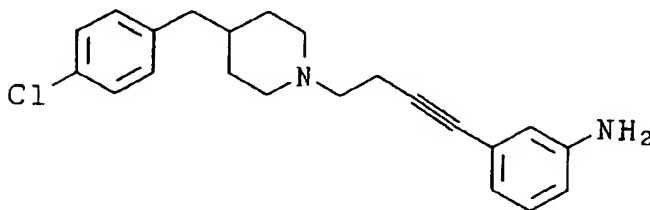
Alternatively, the reagents are mixed in an identical manner except that acetone is used as a solvent, and the mixture is heated at reflux for 16 hr. After cooling, the reaction mixture is filtered and the filtrate evaporated. The residue is purified by silica gel chromatography.



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## Example 3

4- (4-Chloro)benzyl-1-  
[4- (3-aminophenyl)-3-butynyl]-piperidine



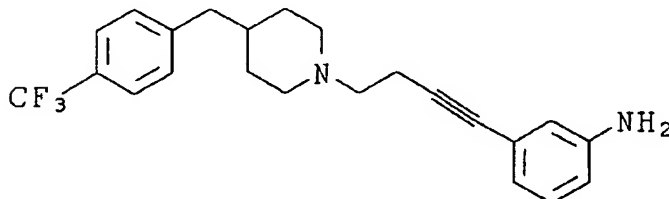
A mixture of 1- (3-butynyl)-4- [(4-chlorophenyl)methyl]piperidine (3.8 mmol), which is prepared according to Example 1, and m-bromoaniline (3.8 mmol) in n-butylamine (20 mL) under a nitrogen atmosphere is treated with tetrakis(triphenylphosphine)palladium (0) (0.17 g) and then heated to reflux for 18 hr. After removing the solvent *in vacuo*, the residue is dissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed with saturated NaHCO<sub>3</sub>. The combined organic solution is dried over magnesium sulfate, filtered and evaporated. The above described product is purified by silica gel chromatography.

Alternatively, a suspension of NaHCO<sub>3</sub> (1 g) and 4- [(4-chlorophenyl)methyl]piperidine (4 mmol) in DMF (25 mL) is stirred under a N<sub>2</sub> atm at 0°C and treated dropwise with 1- [(4-methylphenyl)sulfonyl]oxy-4- (3-amino)phenyl-3-butyne (4 mmol), which is prepared according to Example 5, as a solution in DMF (20 mL). The reaction mixture is heated to 80°C for 12 hr. After cooling, the reaction mixture is stirred vigorously with the addition of water (200 mL) and then extracted with ethyl acetate. The organic layer is dried over magnesium sulfate, filtered and evaporated. The residue is purified by silica gel column chromatography (100:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH) to give the above described product.

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## Example 4

4-(4-Trifluoromethyl)benzyl-1-[4-(3-aminophenyl)-3-butyne]-piperidine



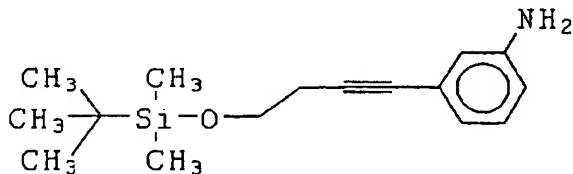
5

A mixture of 1-(3-butyne)-4-[(4-(trifluoromethyl)phenyl)methyl]piperidine (4 mmol), which is prepared according to Example 2, m-iodoaniline (4 mmol) and triethylamine (5 mL) in acetonitrile (50 mL) under a nitrogen atmosphere is treated with bis(triphenylphosphine)palladium (II) chloride (0.5 g). After refluxing for 16 hr, the solvent is removed by rotary evaporation and the above described product purified by silica gel chromatography (100:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH).

20

## Example 5

1-(t-Butyldimethylsiloxy)-4-(3-amino-phenyl)-3-butyne

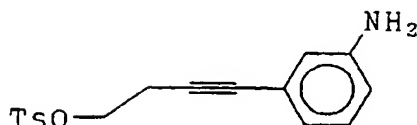


A mixture of 1-(t-butyldimethylsilyloxy)-3-butyne (10 mmol) and m-bromoaniline (10 mmol) in n-butylamine (50 mL) under a nitrogen atmosphere is treated with tetrakis(triphenylphosphine)palladium (0) (0.17 g) and then heated to reflux for 18 hr. After removing the solvent *in vacuo*, the residue is dissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed with saturated NaHCO<sub>3</sub>. The combined organic solution is dried over magnesium sulfate, filtered and evaporated to give the above described silyl protected adduct.

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## Example 6

## 1-tosyl-4-(3-aminophenyl)-3-butyne

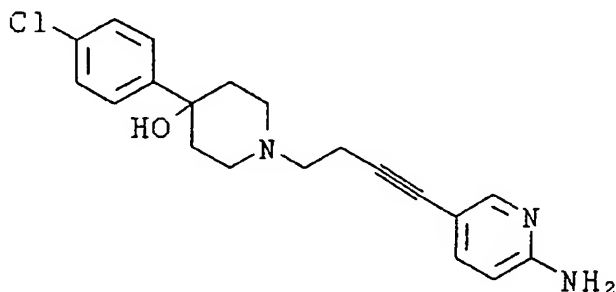


- 5 A solution of 1-(t-butyldimethylsilyloxy)4-(3-aminophenyl)-3-butyne (3 mmol), which is prepared according to Example 5, in  $\text{CH}_2\text{Cl}_2$  (100 mL) is cooled in an ice bath and then treated with tetrabutylammonium
- 10 fluoride (3.1 mmol). After stirring for 30 min, 100 mL water is added, the organic layer partitioned and dried over magnesium sulfate, filtered and evaporated. The residue is dissolved in THF (50 mL) with triethylamine (2 mL) and then treated with tosyl chloride (3 mmol).
- 15 After stirring at room temperature for 4 hr, saturated aqueous NaCl (100 mL) is added and the organic phase partitioned. The aqueous layer is back extracted with methylene chloride. The combined organic layers are dried over magnesium sulfate, filtered and evaporated.
- 20 The above described tosylated product is purified by column chromatography and may be used in a manner similar to that described for Example 2 to prepare 4-substituted piperidine analogs of this invention.

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## Example 7

1-[4-(5-(2-Amino)pyridinyl)-3-butynyl]-  
4-hydroxy-4-(4-chlorophenyl)piperidine



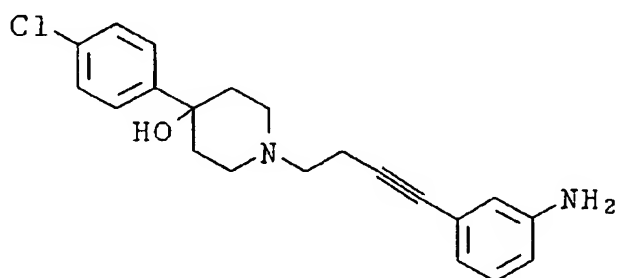
5

The above described product is prepared in a manner similar to that described for Examples 3 or 4.

10

## Example 8

1-[4-(3-Aminophenyl)-3-butynyl]-  
4-hydroxy-4-(4-chlorophenyl)piperidine



15

A) 1-(3-Butynyl)-4-(4-chlorophenyl)-4-hydroxypiperidine. A mixture of 1-mesybut-3-yne (1.48 g, 10.0 mmol), 4-(4-chlorophenyl)-4-hydroxypiperidine (2.54 g, 12.0 mmol) and  $K_2CO_3$  (4.14 g, 30.0 mmol) in  $CH_3CN$  (25 mL) is refluxed for 12 hr. The mixture is filtered and washed with EtOAc (3 x 30 mL). The filtrate is evaporated in vacuo and is purified by flash chromatography to give the product as a colorless solid (2.30 g, 87%): mp 98-100°C;  $^1H$  NMR ( $CDCl_3$ ) 1.55 (s, 1 H), 1.74 (m, 2 H), 1.99 (m, 1 H), 2.10 (m, 2 H), 2.42 (m, 4 H), 2.65 (m, 2 H), 2.79 (m, 2 H), 7.32 (d,  $J$  = 7.2 Hz, 2 H), 7.42 (d,  $J$  = 7.2 Hz, 2 H).

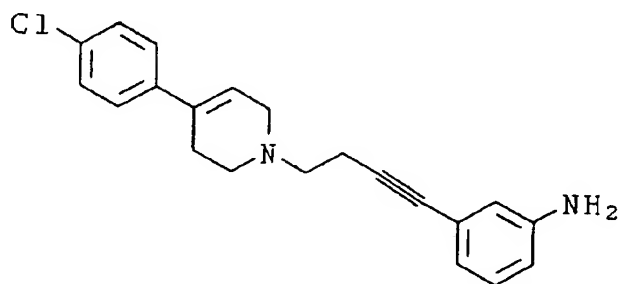
- 62 -

B) 1-(4-(3-Aminophenyl)-3-butynyl)-4-(4-chlorophenyl)-4-hydroxypiperidine. A solution of 1-(3-butynyl)-4-(4-chlorophenyl)-4-hydroxypiperidine (263 mg, 1.00 mmol), 3-iodoaniline (208 mg, 0.950 mmol) and  
5 tetrakis(triphenylphosphine) palladium (0) (46 mg) in n-butylamine (5 mL) is allowed to reflux for 15 hr. The solvent is evaporated in vacuo to give a residue, which is purified by flash chromatography giving the product as an off white solid (231 mg, 69%): mp 139-  
10 140°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.71 (m, 3 H), 2.12 (m, 2 H), 2.56 (m, 4 H), 2.73 (m, 2 H), 2.84 (m, 2 H), 3.60 (bs, 2 H), 6.59 (d, J = 7.5 Hz, 1 H), 6.72 (s, 1 H), 6.79 (d, J = 7.5 Hz, 1 H), 7.07 (dd, J<sub>1</sub> = J<sub>2</sub> = 7.5 Hz, 1 H), 7.33 (d, J = 9.7 Hz, 2 H), 7.46 (d, J = 9.7 Hz, 2 H).

15

## Example 9

1-[4-(3-Aminophenyl)-3-butynyl]-  
20 4-(4-chlorophenyl)-1,2,5,6-tetrahydropyridine



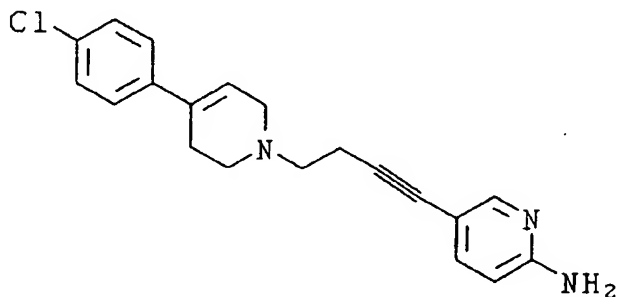
The above described product is prepared in a manner similar to that described for Examples 3 or 4.

25

## Example 10

1 - [4 - (5 - (2-Amino)pyridinyl) - 3-butynyl] -  
4 - (4-chlorophenyl) - 1,2,5,6-tetrahydropyridine

5



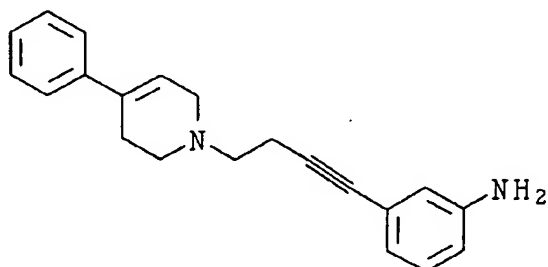
The above described product is prepared in a manner  
similar to that described for Examples 3 or 4.

10

## Example 11

1 - [4 - (3-Aminophenyl) - 3-butynyl] -  
4-phenyl-1,2,5,6-tetrahydropyridine

15



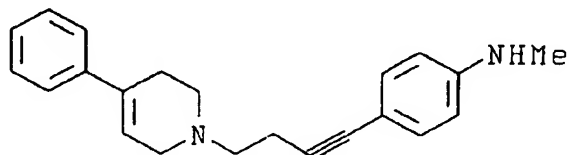
The above described product is prepared in a manner  
similar to that described for Examples 3 or 4.

20

## Example 12

1 - [4 - (4-Methylaminophenyl) - 3-butynyl] -  
4-phenyl-1,2,5,6-tetrahydropyridine

25



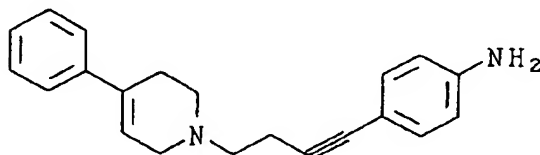
- 64 -

The above described product is prepared in a manner similar to that described for Examples 3 or 4.

## Example 13

5

1-[4-(4-Aminophenyl)-3-butynyl]-  
4-phenyl-1,2,5,6-tetrahydropyridine



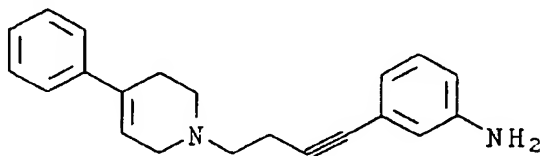
10

The above described product is prepared in a manner similar to that described for Examples 3 or 4.

## Example 14

15

1-[4-(5-Aminophenyl)-3-butynyl]-  
4-phenyl-1,2,5,6-tetrahydropyridine



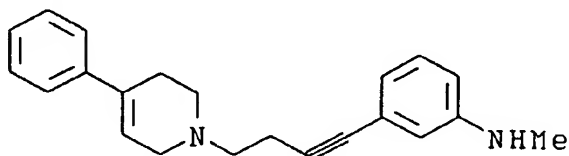
20

The above described product is prepared in a manner similar to that described for Examples 3 or 4.

## Example 15

25

1-[4-(5-Methylaminophenyl)-3-butynyl]-  
4-phenyl-1,2,5,6-tetrahydropyridine



30

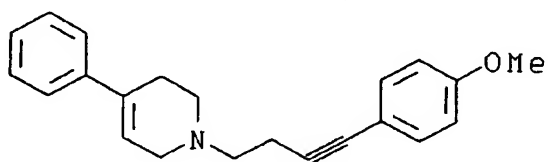
The above described product is prepared in a manner similar to that described for Examples 3 or 4.

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## Example 16

1 - [4 - (4-Methoxyaminophenyl) - 3-butynyl] -  
4-phenyl-1,2,5,6-tetrahydropyridine

5



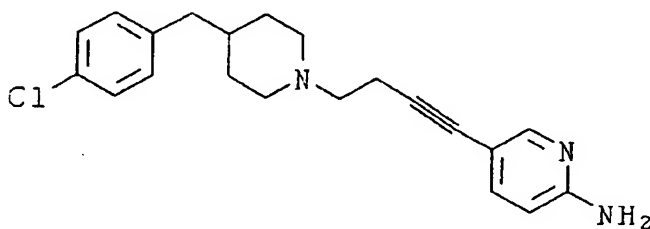
The above described product is prepared in a manner  
similar to that described for Examples 3 or 4.

10

## Example 17

4 - (4-Chloro)benzyl-1-  
[4 - (5 - (2-amino)pyridynyl) - 3-butynyl] - piperidine

15

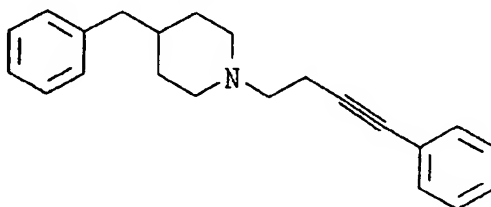


The above described product is prepared in a manner  
similar to that described for Examples 3 or 4.

20

## Example 18

4-Benzyl-1- (4-phenyl-3-butynyl)piperidine



25

A mixture of 1-mesyl-4-phenylbut-3-yne (200 mg, 0.87



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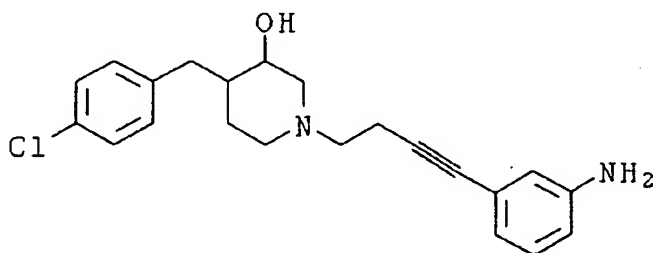
mmol), 4-benzylpiperidine (175 mg, 1.00 mmol) and  $K_2CO_3$  (368 mg, 2.67 mmol) in  $CH_3CN$  (10 mL) is refluxed for 12 hr. The mixture is filtered and washed with EtOAc (3 x 15 mL). The filtrate is evaporated in vacuo and is  
5 purified by flash chromatography to give the product as an oil (100 mg, 38%):  $^1H$  NMR ( $CDCl_3$ ) 1.45 (m, 2 H), 1.52 (m, 1 H), 1.65 (m, 2 H), 2.05 (t,  $J = 6.6$  Hz, 2 H), 2.54 (m, 2 H), 2.68 (m, 4 H), 2.97 (d,  $J = 11$  Hz, 2 H), 7.13-7.36 (m, 10 H).

10

## Example 19

4-(4-Chloro)benzyl-1-[4-(3-aminophenyl)-  
3-butynyl]-3-hydroxypiperidine

15



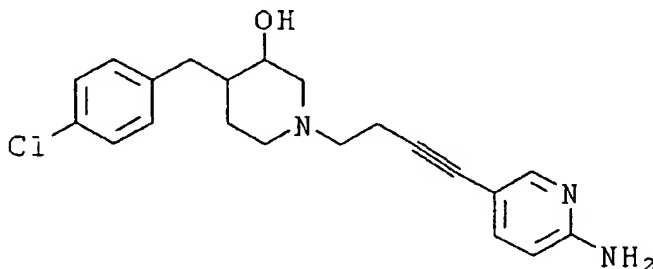
The above described product is prepared in a manner similar to that described for Examples 3 or 4.

20

## Example 20

4-(4-Chloro)benzyl-1-[4-(5-(2-amino)-  
pyridynyl)-3-butynyl]-3-hydroxypiperidine

25



The above described product is prepared in a manner similar to that described for Examples 3 or 4.

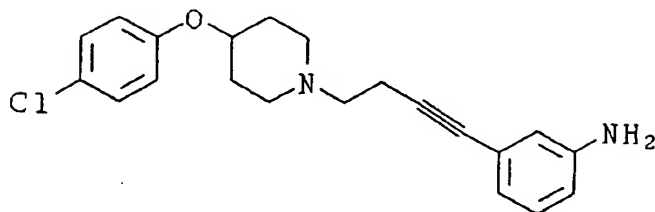
30

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## Example 21

1 - [4 - (3-Aminophenyl) - 3-butynyl] - 4 -  
(4-chloro)phoxypiperidine

5



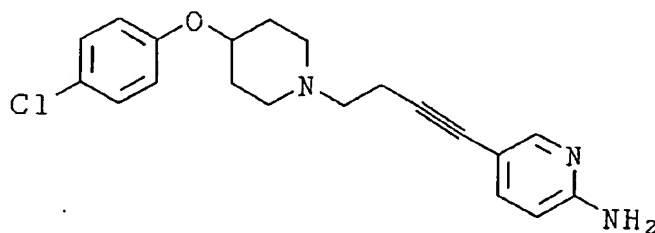
The above described product is prepared in a manner  
similar to that described for Examples 3 or 4.

10

## Example 22

1 - [4 - (5 - (2-Amino)pyridynyl) - 3-butynyl] - 4 -  
(4-chloro)phoxypiperidine

15



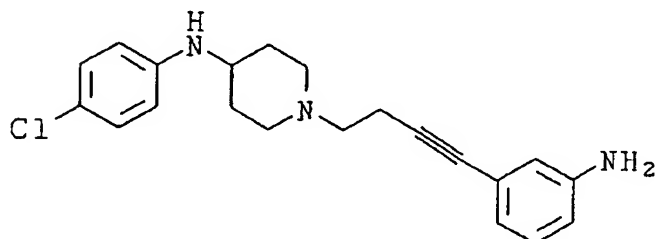
The above described product is prepared in a manner  
similar to that described for Examples 3 or 4.

20

## Example 23

1 - [4 - (3-Aminophenyl) - 3-butynyl] - 4 -  
(4-chlorophenyl)aminopiperidine

25



The above described product is prepared in a manner  
similar to that described for Examples 3 and 4.

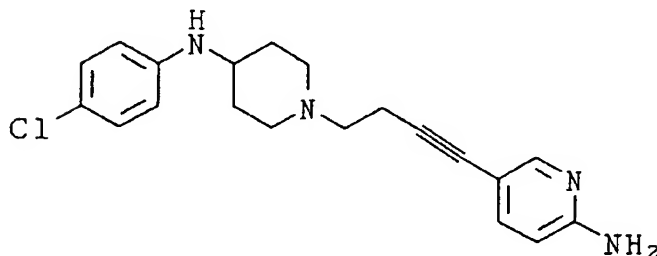
30

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## Example 24

1-[4-(5-(2-Amino)pyridinyl)-3-butyne]-4-(4-chlorophenyl)aminopiperidine

5

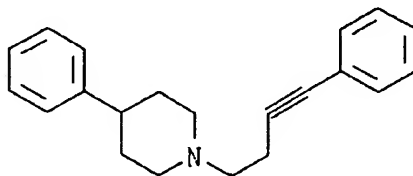


The above described product is prepared in a manner similar to that described for Examples 3 or 4.

10

## Example 25

4-Phenyl-1-(4-phenyl-3-butyne)piperidine



15

- A) 1-Mesylbut-3-yne. Methanesulfonyl chloride (45.8 g, 400 mmol) is added to a stirred solution of 3-butyne-1-ol (14.0 g, 200 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (120 mL) containing 148 mL of pyridine. The resulting solution is allowed to stir at room temperature for 20 hr. The mixture is poured onto ice (50 g). The organic layer is separated and the water phase is extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 30 mL). The combined organic extract is evaporated to remove most of the pyridine.  $\text{CH}_2\text{Cl}_2$  (100 mL) is added to the residue. The resulting solution is washed with 100 mL of 0.5 N HCl solution, 50 mL of cold saturated  $\text{NaHCO}_3$  solution and 30 mL of brine and then is dried over  $\text{Na}_2\text{SO}_4$ . Evaporation of  $\text{CH}_2\text{Cl}_2$  gives the product (22 g, 75%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 2.06 (t,  $J = 2.7$  Hz, 1 H), 2.66 (dt,  $J_1 = 2.7$  Hz,  $J_2 = 6.6$  Hz, 2 H), 4.30 (t,  $J = 6.6$  Hz, 2 H).

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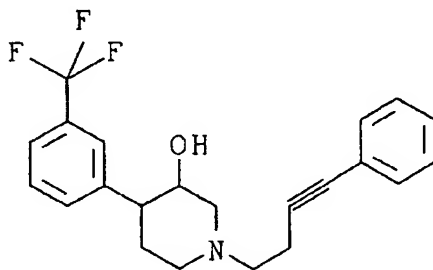
- 69 -

B) 1-Mesyl-4-phenylbut-3-yne. A mixture of 1-mesylbut-3-yne (758 mg, 5.10 mmol), iodobenzene (1.25 g, 6.00 mmol), copper(I) iodide (40 mg),  $\text{PdCl}_2(\text{PPh}_3)_2$  (70 mg) in 12 mL of  $\text{Et}_3\text{N}$  is stirred under  $\text{N}_2$  for 20 hr. The mixture is filtered and washed with  $\text{Et}_3\text{N}$  (3 X 15 mL). The filtrate is evaporated *in vacuo* and is purified by flash chromatography to give the product as a pale yellow oil (560 mg, 50%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 2.91 (t,  $J$  = 6.6 Hz, 2 H), 4.39 (t,  $J$  = 6.6 Hz, 2 H), 7.30 (m, 3 H), 7.38 (m, 2 H).

C) 4-Phenyl-1-(4-phenyl-3-butynyl)piperidine. A mixture of 1-mesyl-4-phenylbut-3-yne (200 mg, 0.870 mmol), 4-phenylpiperidine (120 mg, 0.744 mmol) and  $\text{K}_2\text{CO}_3$  (308 mg, 2.23 mmol) in 10 mL of  $\text{CH}_3\text{CN}$  is refluxed for 12 hr. The mixture is filtered and washed with  $\text{EtOAc}$  (3 x 15 mL). The filtrate is evaporated *in vacuo* and is purified by flash chromatography to give the product (104 mg, 41%): mp 65-66°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 1.81 (m, 4 H), 2.26 (m, 2 H), 2.65 (m, 1 H), 2.69 (m, 2 H), 2.76 (m, 2 H), 3.13 (d,  $J$  = 11 Hz, 2 H), 7.13-7.36 (m, 10 H).

## Example 26

4-(3-(Trifluoromethyl)phenyl)-3-hydroxy-1-(4-phenyl-3-butynyl)piperidine



A mixture of 1-mesyl-4-phenylbut-3-yne (352 mg, 1.57 mmol), 4-(3-(trifluoromethyl)phenyl)piperidin-3-ol hydrochloride (530 mg, 1.88 mmol) and  $\text{K}_2\text{CO}_3$  (542 mg, 3.93 mmol) in 20 mL of  $\text{CH}_3\text{CN}$  is refluxed for 12 hr. The

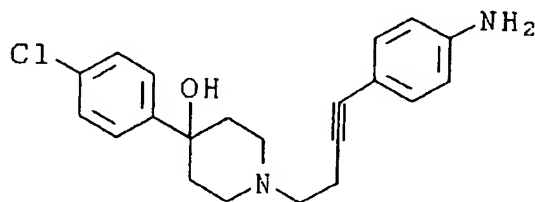
- 70 -

mixture is filtered and washed with EtOAc (3 x 20 mL). The filtrate is evaporated in vacuo and is purified by flash chromatography to give the product as an off white solid (120 mg, 21%): mp 77-79°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)

5 1.71 (m, 2 H), 2.15 (m, 3 H), 2.40 (bs, 1 H), 2.62 (m, 4 H), 2.72 (m, 1 H), 2.83 (m, 2 H), 7.27-7.81 (m, 9 H).

## Example 27

10 1-(4-(4-Aminophenyl)-3-butynyl)-4-(4-chlorophenyl)-4-hydroxypiperidine



A solution of 1-(3-butynyl)-4-(4-chlorophenyl)-4-hydroxypiperidine (263 mg, 1.00 mmol), 4-iodoaniline (208 mg, 0.950 mmol) and 50 mg of tetrakis(triphenylphosphine) palladium in 10 mL of butylamine is allowed to reflux for 20 hr. The solvent is evaporated in vacuo to give a residue, which is

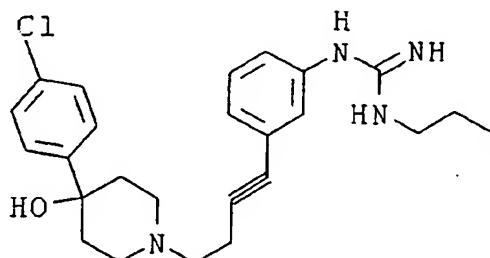
20 purified by flash chromatography giving the product as an off white solid (70 mg, 21%): mp 134-136°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.59 (m, 2 H), 1.90 (m, 2 H), 2.47 (m, 6 H), 2.67 (m, 2 H), 3.59 (s, 1 H), 3.87 (bs, 2 H), 6.46 (d, J = 8.1 Hz, 1 H), 7.02 (d, J = 8.1 Hz, 2 H), 7.14 (d, J = 8.4 Hz, 2 H), 7.33 (d, J = 8.4 Hz, 2 H).

25

## Example 28

N-n-Butyl-N'-(3-(4-(4-(4-chlorophenyl)-4-hydroxy)piperidinyl)butynyl)phenylguanidine

5

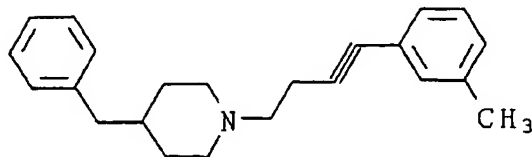


A) 3-Iodophenylcyanamide. To a solution of 3-iodoaniline (3.50 g, 16.0 mmol) in 50 mL of ether is added cyanogen bromide (1.79 g, 16.9 mmol) at 0°C. The resulting mixture is allowed to stir at rt for 12 hr. The solid is collected by filtration and dried *in vacuo* to give the product as a solid (3.32 g, 85%): mp 86-88°C (EtOH/H<sub>2</sub>O); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 6.93 (d, *J* = 8.1 Hz, 1 H), 7.08 (dd, *J*<sub>1</sub> = 7.5 Hz, *J*<sub>2</sub> = 8.1 Hz, 1 H), 7.23 (s, 1 H), 7.34 (d, *J* = 7.5 Hz, 1 H).

B) N-n-Butyl-N'-(3-(4-(4-(4-chlorophenyl)-4-hydroxy)piperidinyl)butynyl)phenylguanidine. A mixture of 1-(3-butynyl)-4-(4-chlorophenyl)-4-hydroxypiperidine (132 mg, 0.500 mmol), 3-iodophenylcyanamide (146 mg, 0.600 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (25 mg, 0.020 mmol) in 5 mL of n-butylamine is allowed to reflux for 12 hr. Evaporation of solvent gives a residue, which is purified by flash chromatography giving the product as a solid (90 mg, 40%): mp 98-100°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 0.93 (m, 5 H), 1.34 (m, 4 H), 1.48 (m, 3 H), 1.71 (m, 3 H), 2.12 (m, 2 H), 2.56 (m, 3 H), 2.76 (m, 1 H), 2.84 (m, 1 H), 3.12 (m, 2 H), 3.75 (bs, 1 H), 6.75-7.46 (m, 8 H). Anal. Calcd for C<sub>26</sub>H<sub>33</sub>ClN<sub>4</sub>O: C, 68.93; H, 7.34; N, 12.37. Found: C, 69.30; H, 7.57; N, 12.00.

## Example 29

## 4-Benzyl-1-(4-(3-methylphenyl)-3-butyryl)piperidine



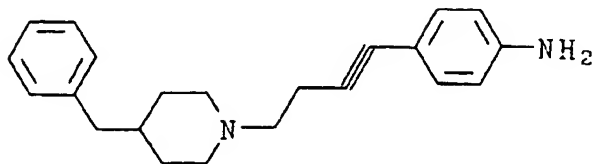
5

- A) 1-Mesyl-4-(3-methylphenyl)but-3-yne. A mixture of 1-mesylbut-3-yne (758 mg, 5.10 mmol), 3-iodotoluene (1.31 g, 6.00 mmol), copper (I) iodide (40 mg),  
10  $\text{PdCl}_2(\text{PPh}_3)_2$  (70 mg) in 12 mL of  $\text{Et}_3\text{N}$  is stirred at room temperature under  $\text{N}_2$  for 20 hr. The mixture is filtered and washed with  $\text{Et}_3\text{N}$  (3 x 15 mL). The filtrate is evaporated in vacuo and is purified by flash chromatography to give the product as a pale yellow oil  
15 (565 mg, 47%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 2.31 (s, 3 H), 2.88 (t,  $J$  = 6.9 Hz, 2 H), 3.07 (s, 3 H), 4.38 (t,  $J$  = 6.9 Hz, 2 H), 7.20 (m, 4 H).

- B) 4-Benzyl-1-(4-(3-methylphenyl)-3-butyryl)piperidine. A mixture of 1-mesyl-4-(3-methylphenyl)but-3-yne (214 mg, 0.900 mmol), 4-benzylpiperidine (189 mg, 1.08 mmol) and  $\text{K}_2\text{CO}_3$  (370 mg, 2.67 mmol) in 10 mL of  $\text{CH}_3\text{CN}$  is refluxed for 12 hr. The mixture is filtered and washed with  $\text{EtOAc}$  (3 x 15 mL).  
25 The filtrate is evaporated in vacuo and is purified by flash chromatography to give the product as an oil (90 mg, 31%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 1.40 (m, 2 H), 1.51 (m, 1 H), 1.65 (m, 2 H), 2.05 (t,  $J$  = 6.6 Hz, 2 H), 2.31 (s, 3 H), 2.54 (m, 2 H), 2.68 (m, 4 H), 2.97 (d,  $J$  = 11.4 Hz, 2 H), 7.13-7.28 (m, 9 H).  
30

## Example 30

## 1-(4-(4-Aminophenyl)-3-butynyl)-4-benzylpiperidine



5

A) 1-(3-Butynyl)-4-benzylpiperidine. A mixture of 1-mesybut-3-yne (3.03 g, 20.0 mmol), 4-benzylpiperidine (4.21 g, 24.0 mmol) and  $K_2CO_3$  (8.28 g, 60.0 mmol) in 50 mL of  $CH_3CN$  is refluxed for 12 hr. The mixture is filtered and washed with EtOAc (3 x 30 mL). The filtrate is evaporated *in vacuo* and is purified by flash chromatography to give the product as pale yellow oil (4.30 g, 95%):  $^1H$  NMR ( $CDCl_3$ ) 1.32 (m, 2 H), 1.51 (m, 1 H), 1.65 (m, 2 H), 1.94 (m, 3 H), 2.36 (m, 2 H), 2.54 (m, 4 H), 2.86 (d,  $J = 11.4$  Hz, 2 H), 7.12-7.27 (m, 5 H).

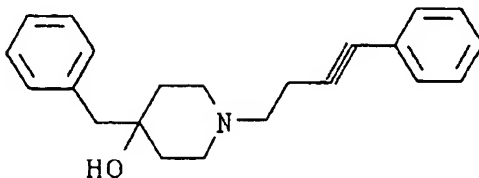
B) 1-(4-(4-Aminophenyl)-3-butynyl)-4-benzylpiperidine. A mixture of 1-(but-3-yn-1-yl)-4-benzylpiperidine (227 mg, 1.00 mmol), 4-iodoaniline (263 mg, 1.20 mmol), copper (I) iodide (15 mg),  $PdCl_2(PPh_3)_2$  (28 mg) in 10 mL of  $Et_3N$  is stirred at room temperature under  $N_2$  for 20 hr. The mixture is filtered and washed with  $Et_3N$  (3 x 15 mL). The filtrate is evaporated *in vacuo* and is purified by flash chromatography to give the product as a pale yellow oil (50 mg, 16%):  $^1H$  NMR ( $CDCl_3$ ) 1.29 (m, 2 H), 1.51 (m, 1 H), 1.66 (m, 2 H), 1.99 (m, 2 H), 2.58 (m, 6 H), 2.91 (m, 2 H), 3.73 (m, 2 H), 6.55 (d,  $J = 7.8$  Hz, 2 H), 7.13-7.28 (m, 7 H).



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## Example 31

## 4-Benzyl-4-hydroxy-1-(4-phenyl-3-butynyl)piperidine



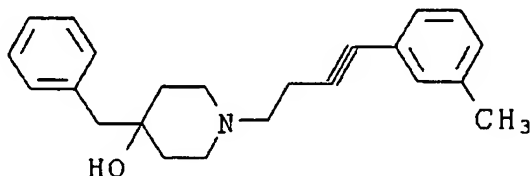
5

A mixture of 1-mesyl-4-phenylbut-3-yne (300 mg, 1.34 mmol), 4-benzyl-4-hydroxypiperidine (307 mg, 1.61 mmol) and  $K_2CO_3$  (555 mg, 4.02 mmol) in 15 mL of  $CH_3CN$  is refluxed for 12 hr. The mixture is filtered and washed with EtOAc (3 x 20 mL). The filtrate is evaporated in vacuo and is purified by flash chromatography to give the product as an off-white solid (130 mg, 30%): mp 80-82°C;  $^1H$  NMR ( $CDCl_3$ ) 1.50 (m, 3 H), 1.74 (m, 2 H), 2.41 (m, 2 H), 2.58 (m, 3 H), 2.75 (m, 5 H), 7.11-7.38 (m, 10 H).

15

## Example 32

## 20 4-Benzyl-4-hydroxy-1-(4-(3-methylphenyl)-3-butynyl)piperidine



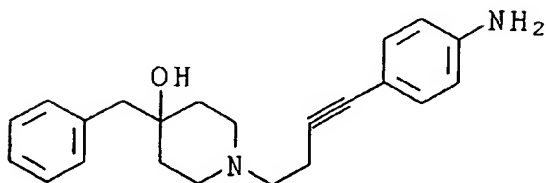
25 A mixture of 1-mesyl-4-(3-methylphenyl)but-3-yne (344 mg, 1.45 mmol), 4-benzyl-4-hydroxy-piperidine (332 mg, 1.73 mmol) and  $K_2CO_3$  (598 mg, 4.34 mmol) in 15 mL of  $CH_3CN$  is refluxed for 12 hr. The mixture is filtered and washed with EtOAc (3 x 20 mL). The filtrate is evaporated in vacuo and is purified by flash chromatography to give the product as a brown oil (100 mg, 20%):  $^1H$  NMR ( $CDCl_3$ ) 1.37 (s, 1 H), 1.55 (m, 2 H), 1.75 (m, 2 H), 2.30 (s, 3 H), 2.41 (m, 2 H), 2.60 (m, 3 H), 2.75 (m, 5 H), 7.11-7.31 (m, 9 H).

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## Example 33

## 1-(4-(4-Aminophenyl)-3-butynyl)-4-benzyl-4-hydroxypiperidine

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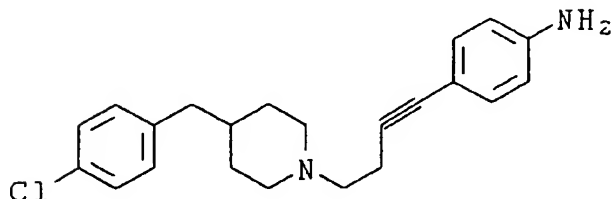
- A) 4-Benzyl-1-(3-butynyl)-4-hydroxypiperidine. A mixture of 1-mesitylbut-3-yne (1.63 g, 11.0 mmol), 4-benzyl-4-hydroxypiperidine (1.91 g, 10.0 mmol) and  $K_2CO_3$  (4.14 g, 30.0 mmol) in 50 mL of  $CH_3CN$  is refluxed for 12 hr. The mixture is filtered and washed with EtOAc (3 x 30 mL). The filtrate is evaporated *in vacuo* and is purified by flash chromatography to give the product as a colorless solid (2.1 g, 86%): mp 51-53°C;  $^1H$  NMR ( $CDCl_3$ ) 1.50 (m, 2 H), 1.65 (m, 3 H), 1.97 (s, 1 H), 2.35 (m, 4 H), 2.62 (m, 4 H), 2.75 (s, 1 H), 7.21-7.31 (m, 5 H).
- 20 B) 1-(4-(4-Aminophenyl)but-3-yn-1-yl)-4-benzyl-4-hydroxypiperidine. A mixture of 4-benzyl-1-(but-3-yn-1-yl)-4-hydroxypiperidine (243 mg, 1.00 mmol), 4-iodoaniline (219 mg, 1.00 mmol), copper(I) iodide (40 mg),  $PdCl_2(PPh_3)_2$  (50 mg, 0.04 mmol) in 10 mL of  $Et_3N$  is stirred at room temperature under  $N_2$  for 20 hr. The mixture is filtered and washed with  $Et_3N$  (3 x 15 mL). The filtrate is evaporated *in vacuo* and is purified by flash chromatography to give the product as a brown oil (100 mg, 30%):  $^1H$  NMR ( $CDCl_3$ ) 1.49 (m, 3 H), 1.72 (m, 2 H), 2.38 (m, 2 H), 2.55-2.66 (m, 6 H), 2.74 (s, 2 H), 3.75 (s, 2 H), 6.52 (d,  $J=8.4$  Hz, 2 H), 7.15-7.30 (m, 7 H).
- 30

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## Example 34

1- (4- (4-Aminophenyl) -3-butynyl) -4-  
(4-chlorobenzyl)piperidine

5



A) 4- (4-Chlorobenzyl) -1- (3-butynyl)piperidine. A mixture of 1-mesybut-3-yne (2.22 g, 15.0 mmol), 4- (4-chlorobenzyl)piperidine hydrochloride (2.95 g, 12.0 mmol), K<sub>2</sub>CO<sub>3</sub> (4.97 g, 36.0 mmol) in 50 mL of CH<sub>3</sub>CN is allowed to reflux for 12 hr. The inorganic salt is removed through a short column of silica gel and washed with EtOAc (3 x 30 mL). Evaporation of solvents gives a residue, which is purified by flash chromatography giving the product as pale yellow oil (2.67 g, 85%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.31 (m, 2 H), 1.50 (m, 1 H), 1.59 (m, 2 H), 1.96 (m, 3 H), 2.38 (m, 2 H), 2.48 (m, 2 H), 2.55 (m, 2 H), 2.88 (d, J = 11.1 Hz, 2 H), 7.04 (d, J = 8.1 Hz, 2 H), 7.26 (d, J = 8.1 Hz, 2 H).

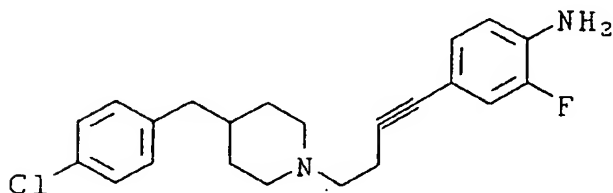
B) 1- (4- (4-Aminophenyl) -3-butynyl) -4- (4-chlorobenzyl)piperidine. To a solution of 4- (4-chlorobenzyl) -1- (but-3-yn-1-yl)piperidine (318 mg, 1.21 mmol) and 4-iodoaniline (265 mg, 2.19 mmol) in 10 mL of butylamine is added 70 mg of Pd(PPh<sub>3</sub>)<sub>4</sub>. The resulting solution is allowed to reflux for 24 hr. The solvent is evaporated in vacuo and the residue is purified by flash chromatography giving the title product as a brown oil (50 mg, 12%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.24 (m, 2 H), 1.44 (m, 1 H), 1.58 (m, 2 H), 1.96 (m, 3 H), 2.15 (m, 2 H), 2.55 (m, 4 H), 2.89 (m, 2 H), 3.75 (bs, 2 H), 6.53 (d, J = 6.0 Hz, 2 H), 7.05 (m, 2 H), 7.20 (m, 4 H).

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## Example 35

1-(4-(4-Amino-3-fluorophenyl)-3-butynyl)  
-4-(4-chlorobenzyl)piperidine

5

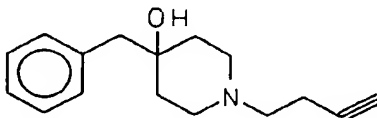


To a solution of 4-(4-chlorobenzyl)-1-(but-3-yn-1-yl)piperidine (400 mg, 1.53 mmol) and 2-fluoro-4-iodoaniline (436 mg, 1.84 mmol) in 10 mL of butylamine is added 70 mg of  $\text{Pd}(\text{PPh}_3)_4$ . The resulting solution is allowed to reflux for 24 hr. The solvent is evaporated in vacuo and the residue is purified by flash chromatography giving the title product as a brown oil (100 mg, 18%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 1.25 (m, 2 H), 1.46 (m, 1 H), 1.58 (m, 2 H), 1.97 (m, 2 H), 2.56 (m, 6 H), 2.88 (m, 2 H), 3.83 (bs, 2 H), 6.62 (m, 1 H), 6.80-7.24 (m, 6 H).

20

## Example 36

4-Benzyl-1-(butynyl)-4-hydroxypiperidine

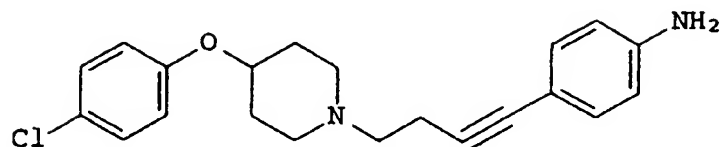


A mixture of 1-mesybut-3-yne (1.63 g, 11.0 mmol), 4-benzyl-4-hydroxypiperidine (1.91 g, 10.0 mmol) and  $\text{K}_2\text{CO}_3$  (4.14g, 30.0 mmol) in 50 mL of  $\text{CH}_3\text{CN}$  is refluxed for 12 hr. The mixture is filtered and is washed with EtOAc (3 X 30 mL). The filtrate is evaporated in vacuo and is purified by flash chromatography to give the product as a colorless solid (2.1 g, 86%): mp 51-53 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 1.50 (m, 2 H), 1.65 (m, 3 H), 1.97 (s, 1 H), 2.35 (m, 4 H), 2.62 (m, 4 H), 2.75 (s, 1 H), 7.21-7.31 (m, 5 H).

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## Example 37

4-{4-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-but-1-ynyl}-phenylamine

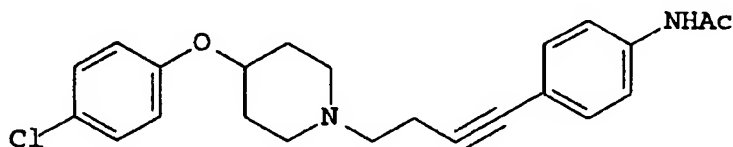


5

The above described product is prepared in a manner similar to that described for Examples 3 or 4.

## Example 38

10 N-{4-[4-(4-Phenoxy-piperidin-1-yl)-but-1-ynyl]-phenyl}-acetamide

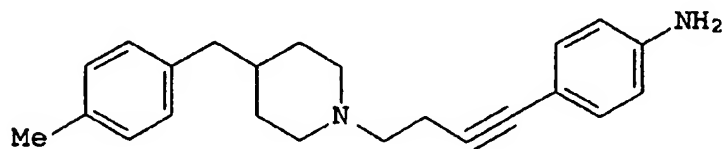


The above described product is prepared in a manner similar to that described for Examples 3 or 4.

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## Example 39

4-{4-[4-(4-Methyl-benzyl)-piperidin-1-yl]-but-1-ynyl}-phenylamine

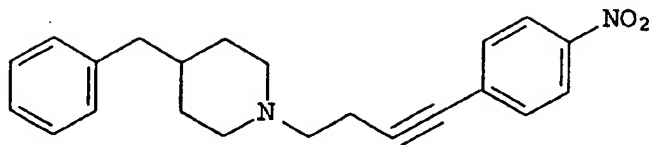


20 The above described product is prepared in a manner similar to that described for Examples 3 or 4.

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## Example 40

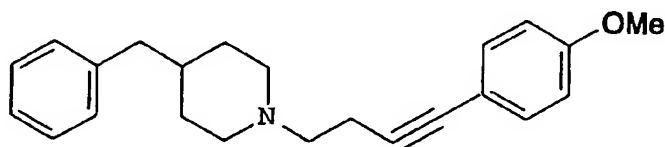
4-Benzyl-1-[4-(4-nitro-phenyl)-but-3-ynyl]-piperidine



The above described product is prepared in a manner  
5 similar to that described for Examples 3 or 4.

## Example 41

4-Benzyl-1-[4-(4-methoxy-phenyl)-but-3-ynyl]-piperidine

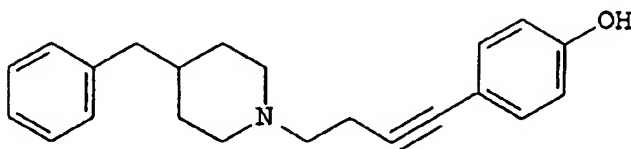


- 10 A mixture of 4-benzyl-1-(but-3-yn-1-yl)piperidine (455  
mg, 2 mmol), 4-iodoanisole (702 mg, 3 mmol) and  
tetrakis(triphenylphosphine)palladium (0) (116 mg, 0.1  
mmol) is stirred in pyrrolidine (5 mL) and deoxygenated  
by bubbling nitrogen through the solution. The mixture  
15 is stirred at room temperature under nitrogen for 20  
hr. The pyrrolidine is evaporated and the residue  
purified by medium pressure liquid chromatography on  
silica gel eluting with 25% to 75% ethyl acetate in  
hexane to give the product as a colorless oil (286 mg,  
20 43%). The oil is stirred in ethanol (10 mL) and oxalic  
acid dihydrate (108 mg) in ethanol (2 mL) added. The  
mixture is allowed to stand in the freezer overnight.  
The salt crystallizes; it is collected, washed with  
cold ethanol and dried at 50°C under high vacuum to  
25 give the title compound as an off-white solid (290 mg):  
mp 158-161°C.

- 80 -

## Example 42

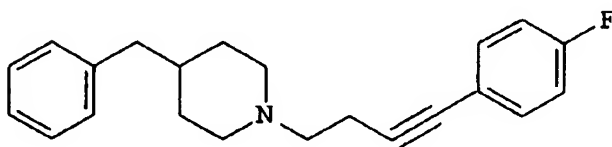
4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenol



The above described product is prepared in a manner  
5 similar to that described for Example 41.

## Example 43

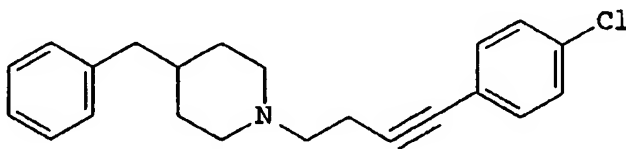
4-Benzyl-1-[4-(4-fluoro-phenyl)-but-3-ynyl]-piperidine



10 The above described product is prepared in a manner  
similar to that described for Example 41.

## Example 44

4-Benzyl-1-[4-(4-chloro-phenyl)-but-3-ynyl]-piperidine

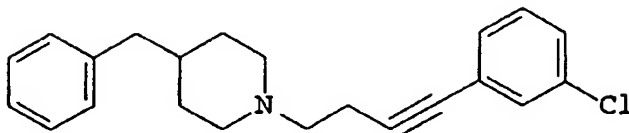


15 The above described product is prepared in a manner  
similar to that described for Example 41.

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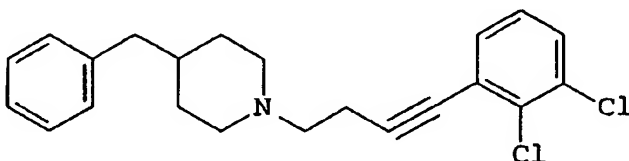
## Example 45

4-Benzyl-1-[4-(3-chloro-phenyl)-but-3-ynyl]-piperidine



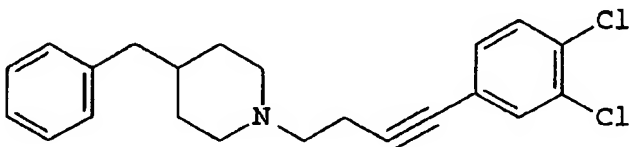
The above described product is prepared in a manner  
5 similar to that described for Example 41.

## Example 46

4-Benzyl-1-[4-(2,3-dichloro-phenyl)-but-3-ynyl]-  
piperidine

10 The above described product is prepared in a manner  
similar to that described for Example 41.

## Example 47

15 4-Benzyl-1-[4-(3,4-dichloro-phenyl)-but-3-ynyl]-  
piperidine

The above described product is prepared in a manner  
similar to that described for Example 41.

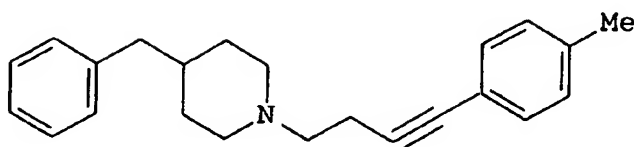
20



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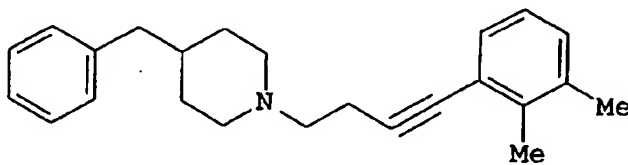
## Example 48

4-Benzyl-1-(4-p-tolyl-but-3-ynyl)-piperidine



The above described product is prepared in a manner  
5 similar to that described for Example 41.

## Example 49

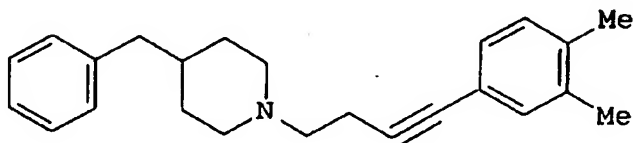
4-Benzyl-1-[4-(2,3-dimethyl-phenyl)-but-3-ynyl]-  
piperidine

10

The above described product is prepared in a manner  
similar to that described for Example 41.

## Example 50

15 4-Benzyl-1-[4-(3,4-dimethyl-phenyl)-but-3-ynyl]-  
piperidine



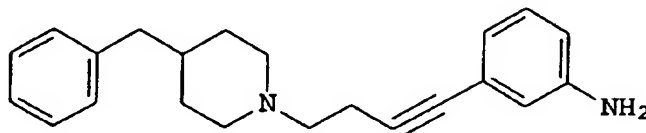
The above described product is prepared in a manner  
similar to that described for Example 41.

20

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## Example 51

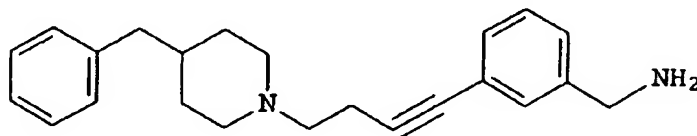
3-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenylamine



The above described product is prepared in a manner  
5 similar to that described for Example 41.

## Example 52

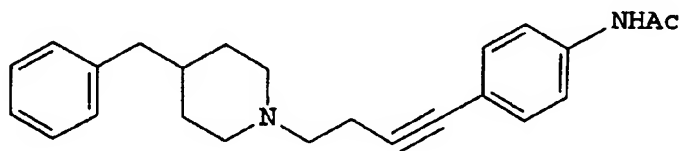
3-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-benzylamine



10 The above described product is prepared in a manner  
similar to that described for Example 41.

## Example 53

15 N-{4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-  
acetamide

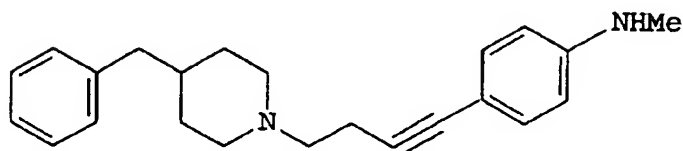


The above described product is prepared in a manner  
similar to that described for Example 41.

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## Example 54

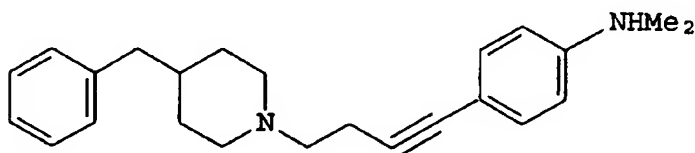
{4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-  
methyl-amine



5 The above described product is prepared in a manner  
similar to that described for Example 41.

## Example 55

10 {4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-  
dimethyl-amine

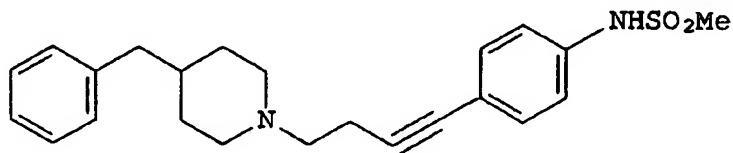


The above described product is prepared in a manner  
similar to that described for Example 41.

15

## Example 56

N-{4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-  
methanesulfonamide

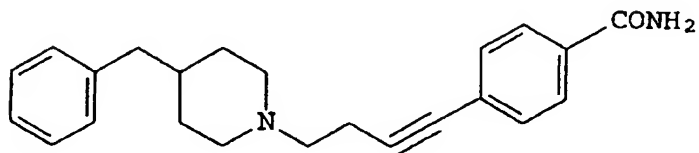


20 The above described product is prepared in a manner  
similar to that described for Example 41.

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## Example 57

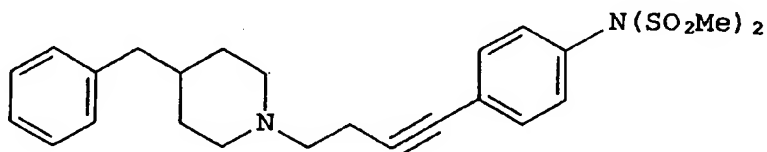
4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-benzamide



The above described product is prepared in a manner  
5 similar to that described for Example 41.

## Example 58

N-(Methylsulfonyl)-N-[4-[4-(phenylmethyl)-1-piperidinyl]-1-butynyl]phenyl-methanesulfonamide

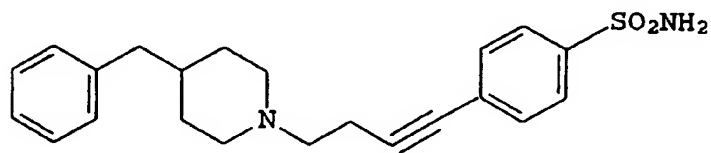


10

The above described product is prepared in a manner  
similar to that described for Example 41.

## Example 59

15 4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-  
benzenesulfonamide



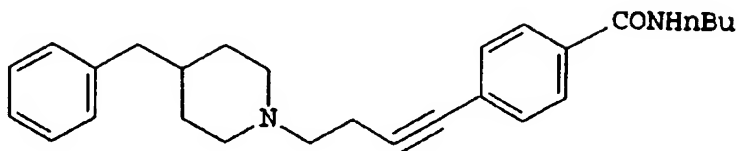
The above described product is prepared in a manner  
similar to that described for Example 41.

20

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## Example 60

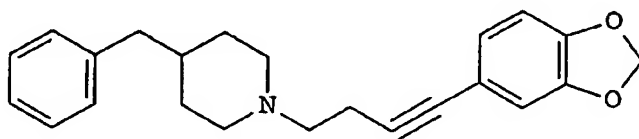
4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-N-butyl-benzamide



5 The above described product is prepared in a manner similar to that described for Example 41.

## Example 61

10 1-(4-Benzo[1,3]dioxol-5-yl-but-3-ynyl)-4-benzyl-piperidine

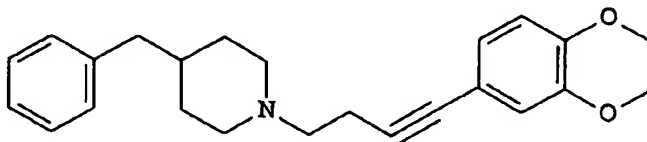


The above described product is prepared in a manner similar to that described for Example 41.

15

## Example 62

4-Benzyl-1-[4-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-but-3-ynyl]-piperidine

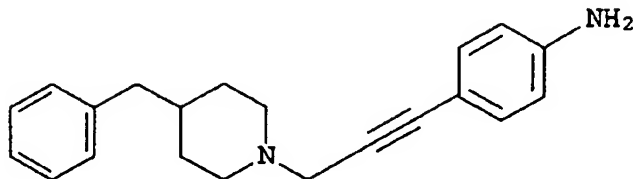


20 The above described product is prepared in a manner similar to that described for Example 41.

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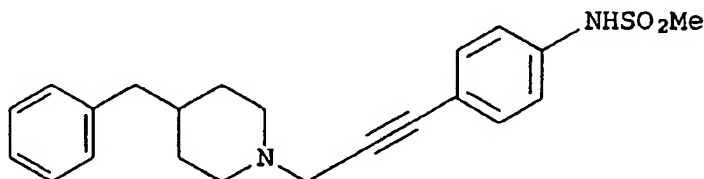
## Example 63

4-[3-(4-Benzyl-piperidin-1-yl)-prop-1-ynyl]-phenylamine



The above described product is prepared in a manner  
5 similar to that described for Example 41.

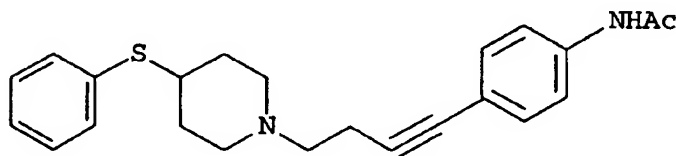
## Example 64

N-{4-[3-(4-Benzyl-piperidin-1-yl)-prop-1-ynyl]-phenyl}-  
methanesulfonamide

10

The above described product is prepared in a manner  
similar to that described for Example 41.

## Example 65

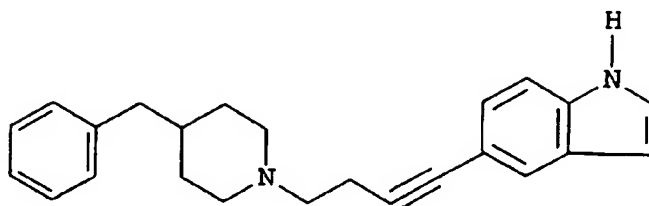
15 N-{4-[4-(4-Phenylsulfanyl-piperidin-1-yl)-but-1-ynyl]-  
phenyl}-acetamide

The above described product is prepared in a manner  
similar to that described for Example 41.

20

## Example 66

5-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-1H-indole



A) 1-Benzenesulfonyl-5-bromoindole. A mixture of 5-bromoindole (5 g, 25.5 mmol) and tetra-n-butylammonium hydrogen sulfate (866 mg, 2.55 mmol) in 50% NaOH (50 mL) and toluene (200 mL) is stirred at room temperature for 5 min. Benzenesulfonyl chloride (3.57 mL, 28 mmol) is added and the mixture stirred for 1 hr. The mixture is diluted with water (500 mL) and extracted with EtOAc (3 x 100 mL). The extracts are washed with brine (250 mL), dried over MgSO<sub>4</sub>, filtered and evaporated to a yellow oil. The oil is purified by medium-pressure column chromatography on silica gel eluting with 10% EtOAc/hexanes to give the title compound as a white solid (7.81 g).

B) 1-Benzenesulfonyl-5-[4-(4-benzyl-piperidin-1-yl)-but-1-ynyl]-1H-indole. A mixture of 1-benzenesulfonyl-5-bromoindole (1.34 g, 4 mmol), 4-benzyl-1-(3-butynyl)-piperidine (908 mg, 4 mmol) and tetrakis(triphenylphosphine)palladium (0) (600 mg) is stirred in pyrrolidine (50 mL) at 50°C under N<sub>2</sub> overnight. Most of the pyrrolidine is evaporated and the residue purified by medium-pressure column chromatography on silica gel eluting with 50% increasing to 100% EtOAc/hexanes to give the title compound as a pale yellow oil (1.55g)

C) 5-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-1H-indole. A mixture of 1-benzenesulfonyl-5-[4-(4-benzyl-

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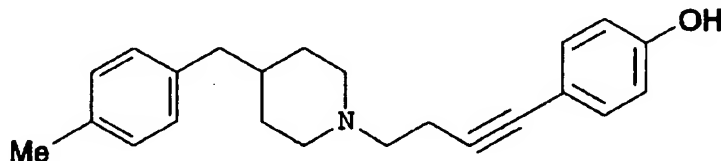
piperidin-1-yl)-but-1-ynyl]-1H-indole (1.49 g, 3.1 mmol) is stirred in EtOH (200 mL) and 50% NaOH (1 mL) at room temperature for 3 days. Most of the EtOH is evaporated and the residue diluted with water (200 mL).

- 5 The precipitate is filtered off and washed copiously with water. The precipitate is recrystallized from hot EtOH to give the title compound as an off-white solid (854 mg): mp 165-166°C.

10

## Example 67

4-{4-[4-(4-Methyl-benzyl)-piperidin-1-yl]-but-1-ynyl}-phenol



- A) 4-(4-Methylbenzyl)-1-(1-butyn-3-yl)piperidine. A mixture of 4-methylbenzylpiperidine hydrochloride (1.129 g, 5.0 mmol), 1-butyn-3-ylmethanesulfonate (0.888 g, 5.0 mmol), and potassium carbonate (2.48 g, 12.5 mmol) in 30 mL of acetonitrile is heated to reflux for 12 hr. The inorganic salt is removed through a short column of silica gel and washed with ethyl acetate (3 x 30 mL). Evaporation of solvents gives a residue, which is purified by flash chromatography (50% EtOAc in hexane), giving 0.96 g (80%) of the title compound as pale yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.26 (m, 3 H), 1.50 (m, 1 H), 1.61 (m, 2 H), 1.96 (m, 2 H), 2.31 (s, 3 H), 2.36 (m, 2 H), 2.47-2.59 (m, 4 H), 2.86 (d, J = 11.4 Hz, 2 H), 7.07 (dd, J<sub>1</sub> = 7.8 Hz, J<sub>2</sub> = 10.5 Hz, 4 H).
- 30 B) 4-{4-[4-(4-Methyl-benzyl)-piperidin-1-yl]-but-1-ynyl}-phenol. To a solution of 4-(4-methylbenzyl)-1-(1-butyn-3-yl)piperidine (400 mg, 1.66 mmol) and 4-iodophenol (347 mg, 1.57 mmol) in 10 mL of butylamine

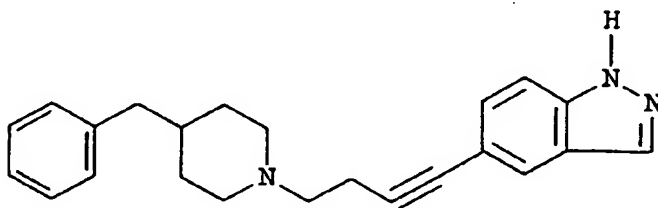


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is added 80 mg of  $\text{Pd}(\text{PPh}_3)_4$ . The resulting solution is allowed to stir at  $55^\circ\text{C}$  for 24 hr. The solvent is evaporated in vacuo and the residue is purified by flash chromatography (20% EtOAc in hexane) to give 150 mg (27%) of the title product as a brown oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 1.34 (m, 2 H), 1.50 (m, 1 H), 1.65 (d,  $J = 11.7$  Hz, 2 H), 2.08 (t,  $J = 12.0$  Hz, 2 H), 2.33 (s, 3 H), 2.47 (d,  $J = 6.9$  Hz, 2 H), 2.60 (t,  $J = 7.2$  Hz, 2 H), 2.68 (t,  $J = 7.5$  Hz, 2 H), 3.02 (d,  $J = 11.1$  Hz, 2 H), 3.49 (brs, 1 H), 6.68 (d,  $J = 8.1$  Hz, 2 H), 7.01 (d,  $J = 7.5$  Hz, 2 H), 7.08 (d,  $J = 7.5$  Hz, 2 H), 7.20 (d,  $J = 8.1$  Hz, 2 H).

## Example 68

15 5-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-1H-indazole

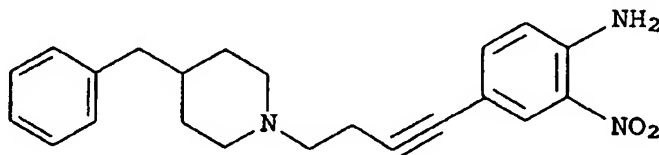


The above described product is prepared in a manner similar to that described for Example 41.

20

## Example 69

4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-2-nitro-phenylamine



A mixture of 4-benzyl-1-(3-butynyl)piperidine (2.27 g, 10 mmol), 4-bromo-2-nitroaniline (2.17 g, 10 mmol) and tetrakis(triphenylphosphine)palladium (0) (600 mg) is stirred in pyrrolidine (50 mL) at  $50^\circ\text{C}$  under  $\text{N}_2$

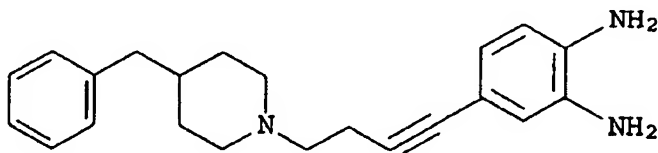
- 91 -

overnight. Most of the pyrrolidine is evaporated and the residue purified by medium-pressure column chromatography on silica gel eluting with 40% increasing to 60% EtOAc/hexanes to give a red oil (3.14 g). A portion of this oil (340 mg) is dissolved in EtOH (8 mL) and oxalic acid dihydrate (126 mg) in EtOH (2 mL) added. On standing at -20°C overnight, the title product monooxalate salt precipitates as an orange solid (200 mg): mp 150-153°C.

10

## Example 70

4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-benzene-1,2-diamine

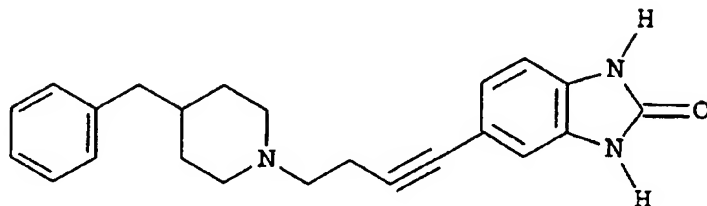


15 4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-2-nitro-phenylamine (crude product, example 69) (2.56 g, 7.0 mmol) is stirred in EtOH (52 mL) and water (8 mL) with conc. HCl (5 drops) and iron filings (3.75 g) at 75°C for 2 hr. The mixture is filtered and evaporated. The  
20 residue is purified by medium-pressure column chromatography on silica gel eluting with 200:8:1 CH<sub>2</sub>Cl<sub>2</sub>:EtOH:NH<sub>4</sub>OH to give the title compound as a beige solid (1.82 g): mp 141-142°C.

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## Example 71

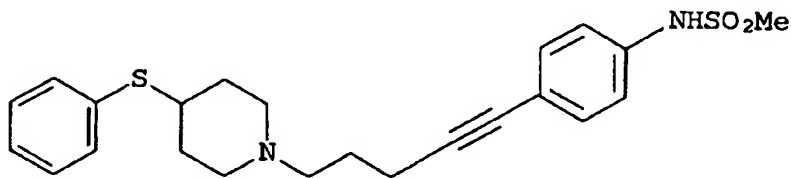
5- [4- (4-Benzyl-piperidin-1-yl) -but-1-ynyl] -1,3-dihydro-benzoimidazol-2-one



- 5 A mixture of 4- [4- (4-benzyl-piperidin-1-yl) -but-1-ynyl] -benzene-1,2-diamine (Example 70) (333 mg, 1 mmol) and carbonyl diimidazole (243 mg, 1.5 mmol) in THF (5 mL) is stirred at room temperature for 1 hr. A precipitate forms; the mixture is diluted with ether  
10 (10 mL), filtered and the solid washed with ether to give the title compound as a white powder (233 mg): mp 221-223°C.

## Example 72

- 15 N- {4- [4- (4-Phenylsulfanyl-piperidin-1-yl) -but-1-ynyl] -phenyl} -methanesulfonamide

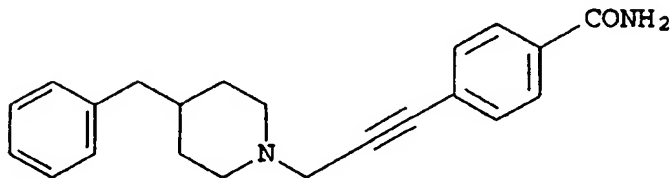


The above described product is prepared in a manner similar to that described for Example 41.

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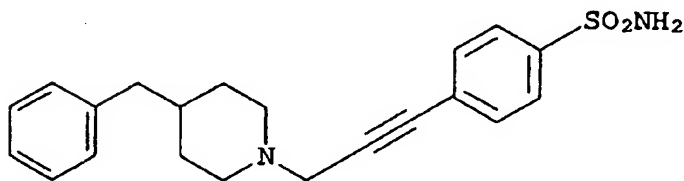
## Example 73

4-[3-(4-Benzyl-piperidin-1-yl)-prop-1-ynyl]-benzamide



The above described product is prepared in a manner  
5 similar to that described for Example 41.

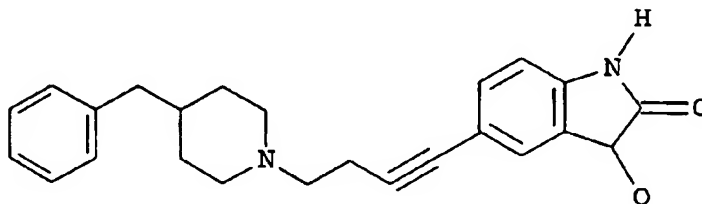
## Example 74

4-[3-(4-Benzyl-piperidin-1-yl)-prop-1-ynyl]-  
benzenesulfonamide

10

The above described product is prepared in a manner  
similar to that described for Example 41.

## Example 75

15 5-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-1H-indole-  
2,3-dione

A mixture of 4-benzyl-1-(3-butynyl)piperidine (904 mg,  
4 mmol), Et<sub>3</sub>N (4 mL), CuI (76 mg, 0.4 mmol) and  
20 Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (41 mg, 0.1 mmol) in DMF (10 mL) is stirred  
at room temperature under N<sub>2</sub> for 30 min. 5-Iodoisatin

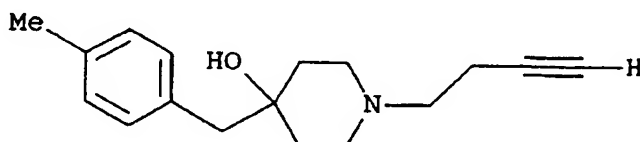
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(546 mg, 2 mmol) is added and stirring continued overnight. The mixture is evaporated and the residue purified by medium-pressure column chromatography on silica gel eluting with 50% EtOAc/hexanes (+ 1% Et<sub>3</sub>N) to give an orange solid (238 mg). The solid is recrystallized from hot 90:10 isopropanol:water to give the title compound as orange crystals (152 mg): mp 140-141°C

10

## Example 76

4-(4-Methylbenzyl)-4-hydroxy-1-(but-3-yn-1-yl)  
piperidine

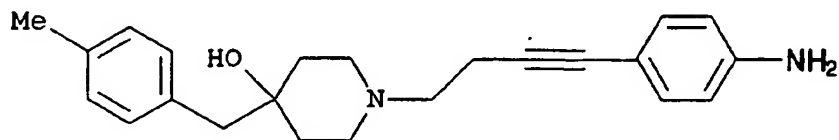


A mixture of 4-methyl-4-hydroxybenzylpiperidine hydrochloride (1.3 g, 5.4 mmol), 1-butyn-4-yl methanesulfonate (0.96 g, 6.5 mmol), potassium carbonate (2.5 g, 18 mmol) in 50 mL of acetonitrile was allowed to reflux for 12 hrs. The inorganic salt was removed through a short column of silica gel and washed with ethyl acetate (3 x 30 mL). Evaporation of solvents gave a residue, which was purified by flash chromatography (50% EtOAc in hexane), giving 0.90 g (65%) of the title compound as a pale yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.258 (m, 2 H), 1.883 (m, 2 H), 1.962 (m, 3 H), 2.040 (m, 2 H), 2.342 (s, 3 H), 2.399 (m, 2 H), 2.611 (m, 3 H), 2.708 (m, 2 H), 7.060-7.135 (m, 4 H).

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## Example 77

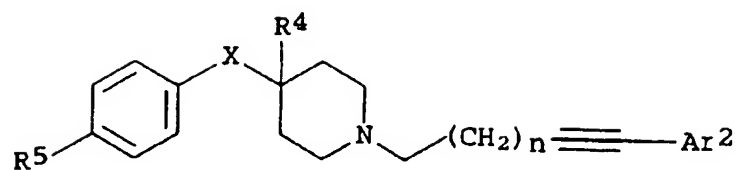
1- (1- (4-Aminophenyl) -1-butyn-4-yl) -4-hydroxy-4-  
(4-methylbenzyl)piperidine



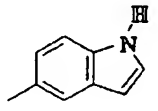
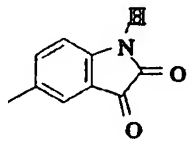
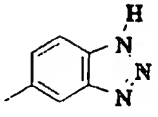
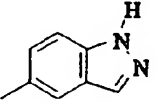
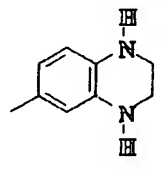
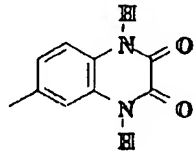
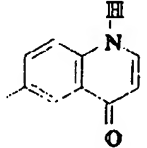
- 5 To a solution of 4-hydroxy-4- (4-methylbenzyl) -1- (1-but-  
3-yn-1-yl) piperidine (450 mg. 1.75 mmol) and 4-  
iodoaniline (383 mg., 1.75 mmol) in 15 mL. of  
pyrrolidine was added 75 mg of Pd(PPh<sub>3</sub>)<sub>4</sub>. The resulting  
solution was allowed to stir at rt for 24 h. The  
10 solvent was evaporated in vacuo and the residue was  
purified by flash chromatography (20% EtOAc in hexane),  
giving 325 mg (54%) of the title compound as a brown  
oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.647 (m, 3 H), 1.880 (m, 2 H),  
2.046 (m, 2 H), 2.326 (s, 3 H), 2.592 (m, 2 H), s.712  
15 (m, 4 H), 2.454 (m, 4 H), 3.729 (s, 2 H), 6.578 (m,  
2 H), 7.107-7.190 (m, 6 H).

By following the general procedures set forth above,  
the additional inventive compounds shown in Tables 1  
20 and 2 can be prepared.

Table 1



Example	$R^5$	X	$R^4$	n	$Ar^2$
78	H	$CH_2$	H	1	
79	F	S	H	1	
80	Me	O	H	2	
81	Cl	S	H	2	
82	MeO	$CH_2$	OH	1	

	83	F	CH <sub>2</sub>	H	3	
5	84	Et	O	H	1	
	85	Cl	O	H	2	
10	86	Me	CH <sub>2</sub>	H	1	
15	87	H	S	H	3	
	88	MeO	CH <sub>2</sub>	OH	2	
20	89	F	O	H	1	



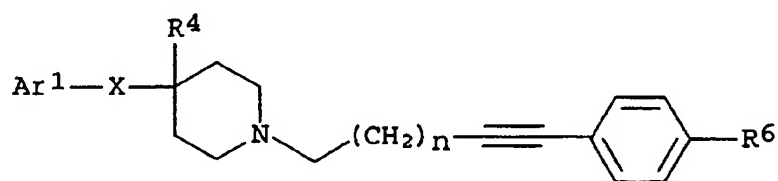
	90	F	CH <sub>2</sub>	H	0	
5	91	Cl	CH <sub>2</sub>	H	1	
	92	i-Pr	CH <sub>2</sub>	OH	2	
10	93	Me	S	H	3	
	94	OH	-	H	2	
15	95	H	CH <sub>2</sub>	OH	1	

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96	Cl	O	H	1	
97	F	CH <sub>2</sub>	H	2	

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Table 2



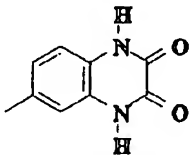
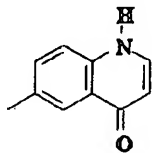
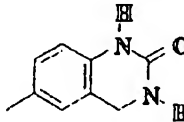
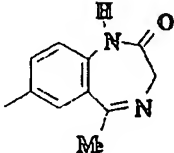
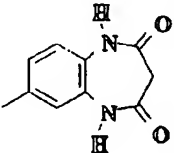
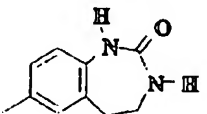
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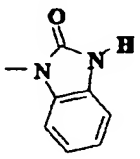
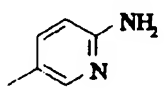
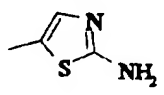
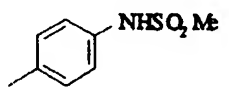
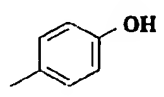
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Example	Ar <sup>1</sup>	X	R <sup>4</sup>	n	R <sup>6</sup>
98		CH <sub>2</sub>	H	1	H
99		S	H	1	F
100		-	H	2	Me

101		S	H	2	Cl
102		-	OH	1	MeO
103		-	H	3	F
104		O	H	1	Et
105		-	H	2	Cl
106		CH <sub>2</sub>	H	1	Me
107		S	H	3	H

5     10   15	108		-	OH	2	MeO
	109		O	H	1	F
	110		CH <sub>2</sub>	H	0	F
	111		-	H	1	Cl
	112		CH <sub>2</sub>	OH	2	i-Pr
	113		S	H	3	Me

5     10     15     20	114		-	H	2	OH
	115		CH <sub>2</sub>	OH	1	H
	116		O	H	1	Cl
	117		-	H	2	F
	118		-	OH	1	Cl
	119		CH <sub>2</sub>	OH	2	H

The potency of antagonism for the compounds of Examples 1, 7, 8, 11-16, 18, 25-35 and 37-77 described above in the expressed cloned NMDA subtypes and their anti-convulsant activity against maximal electroshock are shown below in Table 3.

Table 3

	Compound	Subunits (IC <sub>50</sub> (μM))				MES (ED <sub>50</sub> ) mg/kg
		1A/2A	1A/2B	1A/2C	1A/2D	
5	Ex. 1	150	1.3	>300		
	Ex. 7	>100	3	>100	>100	
	Ex. 8	>100	6	>100	>100	10.0
	Ex. 11	>100	8.5	>100	>100	
	Ex. 12	50	14	>100	>100	
10	Ex. 13	90	22	>100	>100	
	Ex. 14	40	30	>100	>100	
	Ex. 15	90	30	>100	>100	
	Ex. 16	85	45	>100	>100	
	Ex. 18	>100	3	>100		3.5
15	Ex. 25	40	14	>100		
	Ex. 26	21	5			
	Ex. 27	60	4	>100		
	Ex. 28	16	2	30		10.0
	Ex. 29	>100	1.8	>100		
20	Ex. 30	>100	0.33	>100		1.8
	Ex. 31	>100	2	>100		
	Ex. 32	75	3.4	>100		
	Ex. 33	100	0.9	>100		
	Ex. 34	>100	0.6	>100		
25	Ex. 35	>100	0.6	>100		
	Ex. 37	120	3.30	>300		
	Ex. 38	>300	35.0	>300		
	Ex. 39	70.0	0.35	>300		2.5
	Ex. 40	120	5.00	>300		
30	Ex. 41	130	3.00	250		
	Ex. 42	>300	0.14	>300		2.5
	Ex. 43	100	2.10	>300		
	Ex. 44	45.0	5.00	105		

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5	Ex. 45	170	2.60	>300		
	Ex. 46	>300	6.00	>300		
	Ex. 47	160	120	>300		
	Ex. 48	45.0	3.20	>300		
	Ex. 49	>300	37.0	>300		
10	Ex. 50	300	3.00	>300		
	Ex. 51	>300	1.20	>300		
	Ex. 52	15.0	0.40	200		
	Ex. 53	>300	0.45	>300		8.0
	Ex. 54	60.0	0.20	>300		6.5
15	Ex. 55	200	23.0	>300		
	Ex. 56	150	0.20	150		>5
	Ex. 57	150	3.00	300		
	Ex. 58	>300	40.0	>300		
	Ex. 59	21.0	0.70	>300		>5
20	Ex. 60	>300	20.0	>300		
	Ex. 61	70.0	15.0	>300		
	Ex. 62	160	18.0	270		
	Ex. 63	180	12.0	>300		
	Ex. 64	>300	0.37	>300		
25	Ex. 65	>300	1.40	>300		
	Ex. 66	170	1.00	180		
	Ex. 67	70.0	0.70	58.0		6.0
	Ex. 68		0.35			
	Ex. 69		0.25			
30	Ex. 70		0.18			
	Ex. 71		0.10			
	Ex. 72		0.40			
	Ex. 73		30.0			
	Ex. 74		80.0			
30	Ex. 75		2.00			
	Ex. 76	280	1.0	>300		
	Ex. 77	70	0.4	>300		0.4

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#	5	2.9	3		
##	>100	8.5	>100		
5 # N-4-(1-(4-(3-aminophenyl)butyn-3-yl)piperidinyl)-2-oxobenzimidazol;  ## -1-(4-(2-aminophenyl)-3-butynyl)-4-phenylpiperidine					

10 The data are the mean  $IC_{50}$  values ( $\mu M$ ) for inhibition of NMDA-activated membrane current responses. The data show that 4-substituted piperidine analogs of this invention exhibit selectivity for 2B subtype receptors compared to 2A, 2C and 2D subtype receptors.

15

In addition, compounds 8, 18, 28, 30, 39, 42, 53, 54 and 67 also demonstrated potent activity against maximal electroshock (MES) as shown in Table 3.

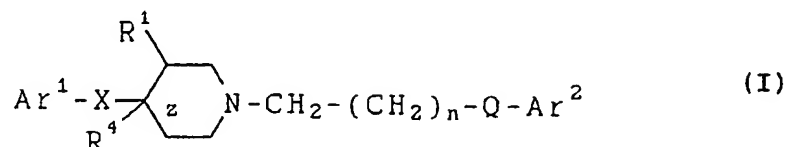
20 Other variations and modifications of this invention will be obvious to those skilled in this art. This invention is not limited except as set forth in the following claims.

25



## WHAT IS CLAIMED IS:

1. A compound represented by the formula (I)



or a pharmaceutically acceptable salt thereof wherein

$\text{Ar}^1$  and  $\text{Ar}^2$  are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an alkylguanidine group, a lower alkyl amino group or a lower alkoxy group;

$z$  is a single or double bond;

$\text{X}$  is  $-(\text{CHR}^2)_m-$ , O, S or  $\text{NR}^3$ , wherein each  $\text{R}^2$  is independently hydrogen, hydroxy, lower alkoxy or a lower alkyl group having 1 to 6 carbon atoms and  $m$  is 0, 1 or 2, and  $\text{R}^3$  is hydrogen or a lower alkyl group having 1 to 6 carbon atoms, provided that when  $z$  is a double bond then  $\text{X}$  is not O, S or  $\text{NR}^3$ ;

$\text{R}^1$  is hydrogen or hydroxy;

$n$  is 0, 1 or 2;

$\text{Q}$  is  $-\text{CH}=\text{CH}-$  or  $-\text{C}\equiv\text{C}-$ ; and

$\text{R}^4$  is hydrogen or hydroxy when  $z$  is a single bond provided that (i) when  $n$  is 0, then  $z$  is a double bond and  $\text{R}^4$  is not present, (ii) when  $n$  is 1 or 2 and  $\text{Q}$  is  $-\text{C}\equiv\text{C}-$  and  $z$  is a double bond or  $\text{R}^4$  is hydroxy, then  $\text{Ar}^1$  is aryl substituted by halogen and (iii) when  $\text{R}^4$  is hydroxy then  $\text{R}^2$  is not hydroxy or lower alkoxy.

2. A compound according to claim 1, wherein  $\text{Q}$  is  $-\text{C}\equiv\text{C}-$ .

3. A compound according to claim 2, wherein  $\text{Ar}^2$  is a pyridynyl or a phenyl group, either of which is

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unsubstituted or substituted by halogen, amino or lower alkyl amino.

4. A compound according to claim 3, wherein Ar<sup>1</sup> is substituted or unsubstituted phenyl.

5. A compound according to claim 4, wherein Ar<sup>2</sup> is selected from the group consisting of 2-amino pyridynyl, 2-aminophenyl, 3-aminophenyl and 4-aminophenyl.

6. A compound according to claim 5, wherein Ar<sup>1</sup> is a halophenyl group.

7. A compound according to claim 1, said compound selected from the group consisting of:

1-[4-(3-Aminophenyl)-3-butynyl]-4-hydroxy-4-(4-chlorophenyl)piperidine;

1-[4-(5-(2-Amino)pyridynyl)-3-butynyl]-4-hydroxy-4-(4-chlorophenyl)piperidine;

1-[4-(4-Fluorophenyl)-3-butynyl]-4-hydroxy-4-(4-chlorophenyl)piperidine;

1-[5-(3-Aminophenyl)-4-pentynyl]-4-hydroxy-4-(4-chlorophenyl)piperidine;

1-[4-(3-Aminophenyl)-3-butynyl]-4-(4-chlorophenyl)-1,2,5,6-tetrahydropyridine;

1-[4-(5-(2-Amino)pyridynyl)-3-butynyl]-4-(4-chlorophenyl)-1,2,5,6-tetrahydropyridine;

1-[4-(4-Fluorophenyl)-3-butynyl]-4-(4-chlorophenyl)-1,2,5,6-tetrahydropyridine;

1-[5-(3-Aminophenyl)-4-pentynyl]-4-(4-chlorophenyl)-1,2,5,6-tetrahydropyridine;

4-Benzyl-1-[4-(3-aminophenyl)-3-butynyl]piperidine;

4-Benzyl-1-(4-phenyl-3-butynyl)piperidine;

4-(4-Chloro)benzyl-1-[4-(3-aminophenyl)-3-butynyl]piperidine;

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4- (4-Chloro)benzyl-1- [4- (4-hydroxyphenyl-3-butynyl)]piperidine;

4- (4-Chloro)benzyl-1- [4- (5- (2-amino)pyridynyl)-3-butynyl]-piperidine;

1- [4- (4-Fluorophenyl)-3-butynyl]-4- (3-trifluoromethylbenzyl)-piperidine;

4- (4-Chlorobenzyl)-1- [5- (3-aminophenyl)-4-pentynyl]-piperidine;

4-Benzyl-1- [4- (3-aminophenyl)-3-butynyl]-3-hydroxypiperidine;

4-Benzyl-1- (4-phenyl-3-butynyl)-3-hydroxypiperidine;

4- (4-Chloro)benzyl-1- [4- (3-aminophenyl)-3-butynyl]3-hydroxypiperidine;

4- (4-Chloro)benzyl-1- [4- (5- (2-amino)pyridynyl)-3-butynyl]-3-hydroxypiperidine;

1- [4- (4-Fluorophenyl)-3-butynyl]-4- (3-trifluoromethylbenzyl)-3-hydroxy-piperidine;

4- (4-Chlorobenzyl)-3-hydroxy-1- [5- (3-aminophenyl)-4-pentynyl]-piperidine;

1- [4- (3-Aminophenyl)-3-butynyl]-4-phenoxy-piperidine;

1- (4-Phenyl-3-butynyl)-4-phenoxy-piperidine;

1- [4- (3-Aminophenyl)-3-butynyl]-4- (4-chloro)phenoxy-piperidine;

1- [4- (5- (2-Amino)pyridynyl)-4-butynyl]-4- (4-chloro)phenoxy-piperidine;

1- [4- (4-Fluorophenyl)-3-butynyl]-4- (3-trifluoromethyl)phenoxy-piperidine;

1- [5- (3-Aminophenyl)-4-pentynyl]-4- (4-chloro)phenoxy-piperidine;

1- [4- (3-Aminophenyl)-3-butynyl]-4- (phenyl)aminopiperidine;

1- (4-Phenyl-3-butynyl)-4- (phenyl)aminopiperidine;

1- [4- (3-Aminophenyl)-3-butynyl]-4- (4-chlorophenyl)aminopiperidine;

1- [4- (5- (2-Amino)pyridynyl) -3-butynyl] -4- (4-chlorophenyl) aminopiperidine;

1- [4- (4-Fluorophenyl) -3-butynyl] -4- (3-trifluoromethylphenyl) aminopiperidine;

1- (4- (4-Amino-3-fluorophenyl) -3-butynyl) -4- (4-chlorobenzyl) piperidine;

1- [5- (3-Aminophenyl) -4-pentynyl] -4- (4-chlorophenyl) aminopiperidine;

4-Phenyl-1- (4-phenyl-3-butynyl) piperidine;

4- (3- (Trifluoromethyl)phenyl) -3-hydroxy-1- (4-phenyl-3-butynyl) piperidine;

1- (4- (4-Aminophenyl) -3-butynyl) -4- (4-chlorophenyl) -4-hydroxypiperidine;

N-n-Butyl-N' - (3- (4- (4- (4-chlorophenyl) -4-hydroxy) piperidinyl) butynyl) phenylguanidine;

4-Benzyl-1- (4- (3-methylphenyl) -3-butynyl) piperidine;

1- (4- (4-Aminophenyl) -3-butynyl) -4-benzyl-4-hydroxypiperidine;

1- (4- (4-Aminophenyl) -3-butynyl) -4- (4-chlorobenzyl) piperidine;

N-4- (1- (4- (3-Aminophenyl) butyn-3-yl) piperidinyl) -2-oxobenzimidazol;

1- (4- (2-Aminophenyl) -3-butynyl) -4-phenylpiperidine;

4- {4- [4- (4-Chloro-phenoxy) -piperidin-1-yl] -but-1-ynyl} -phenylamine;

N- {4- [4- (4-Phenoxy-piperidin-1-yl) -but-1-ynyl] -phenyl} -acetamide;

4- {4- [4- (4-Methyl-benzyl) -piperidin-1-yl] -but-1-ynyl} -phenylamine;

4-Benzyl-1- [4- (4-nitro-phenyl) -but-3-ynyl] -piperidine;

4-Benzyl-1- [4- (4-methoxy-phenyl) -but-3-ynyl] -piperidine;

4- {4- (4-Benzyl-piperidin-1-yl) -but-1-ynyl} -phenol;

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4-Benzyl-1-[4-(4-fluoro-phenyl)-but-3-ynyl]-piperidine;

4-Benzyl-1-[4-(4-chloro-phenyl)-but-3-ynyl]-piperidine;

4-Benzyl-1-[4-(3-chloro-phenyl)-but-3-ynyl]-piperidine;

4-Benzyl-1-[4-(2,3-dichloro-phenyl)-but-3-ynyl]-piperidine;

4-Benzyl-1-[4-(3,4-dichloro-phenyl)-but-3-ynyl]-piperidine;

4-Benzyl-1-(4-p-tolyl-but-3-ynyl)-piperidine;

4-Benzyl-1-[4-(2,3-dimethyl-phenyl)-but-3-ynyl]-piperidine;

4-Benzyl-1-[4-(3,4-dimethyl-phenyl)-but-3-ynyl]-piperidine;

3-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenylamine;

3-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-benzylamine;

N-{4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-acetamide;

{4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-methyl-amine;

{4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-dimethyl-amine;

N-{4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-methanesulfonamide;

4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-benzamide;

N-(Methylsulfonyl)-N-{4-[4-(4-(phenylmethyl)-1-piperidinyl)-1-butynyl]phenyl}-methanesulfonamide;

4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-benzenesulfonamide;

4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-N-butylbenzamide;

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1-(4-Benzo[1,3]dioxol-5-yl-but-3-ynyl)-4-benzyl-piperidine;

4-Benzyl-1-[4-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-but-3-ynyl]-piperidine;

4-[3-(4-Benzyl-piperidin-1-yl)-prop-1-ynyl]-phenylamine;

N-{4-[3-(4-Benzyl-piperidin-1-yl)-prop-1-ynyl]-phenyl}-methanesulfonamide;

N-{4-[4-(4-Phenylsulfanyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-acetamide;

5-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-1H-indole;

4-{4-[4-(4-Methyl-benzyl)-piperidin-1-yl]-but-1-ynyl}-phenol;

5-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-1H-indazole;

4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-2-nitro-phenylamine;

4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-benzene-1,2-diamine;

5-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-1,3-dihydro-benzoimidazol-2-one;

N-{4-[4-(4-Phenylsulfanyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-methanesulfonamide;

4-[3-(4-Benzyl-piperidin-1-yl)-prop-1-ynyl]-benzamide;

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4-[3-(4-Benzyl-piperidin-1-yl)-prop-1-ynyl]-benzenesulfonamide;

5-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-1H-indole-2,3-dione;

4-benzyl-4-hydroxy-1-4-(-3-methylphenyl)-3-butynyl)piperidine;

4-benzyl-4-hydroxy-1-(4-phenyl-3-butynyl)piperidine;

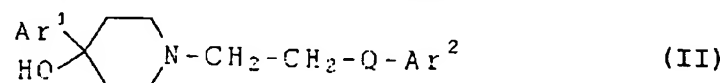
4-benzyl-4-hydroxy-1-(4-(4-aminophenyl)-3-butynyl)piperidine; and

4-(4-methylbenzyl)-4-hydroxy-1-(4-(4-aminophenyl)-3-butynyl)piperidine, and

a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition useful for treating disorders responsive to the selective blockade of N-methyl-D-aspartate receptor subtypes such as stroke, cerebral ischemia, central nervous systems, trauma, hypoglycemia, neurodegenerative disorders, anxiety, migraine headaches, convulsions, aminoglycoside antibiotics-induced hearing loss, chronic pain, psychosis, glaucoma, CMV retinitis, opioid tolerance or withdrawal or urinary incontinence, said compositions comprising a pharmaceutically acceptable carrier or diluent and a therapeutically effective amount of at least one compound of claim 1.

9. A compound represented by the formula:



or a pharmaceutically acceptable salt thereof wherein:

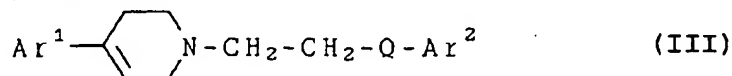
Ar<sup>1</sup> and Ar<sup>2</sup> are independently aryl or a heteroaryl group, either of which may be independently substituted

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by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an alkylguanidine group, a lower alkyl amino group or a lower alkoxy group; and

Q is -CH=CH- or -C≡C-, provided that when Q is -C≡C- then Ar<sup>1</sup> is aryl substituted by halogen.

10. A compound represented by the formula:

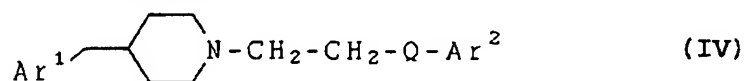


or a pharmaceutically acceptable salt thereof wherein:

Ar<sup>1</sup> and Ar<sup>2</sup> are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an alkylguanidine group, a lower alkyl amino group or a lower alkoxy group; and

Q is -CH=CH- or -C≡C-, provided that when Q is -C≡C- then Ar<sup>1</sup> is aryl substituted by halogen..

11. A compound represented by the formula:



or a pharmaceutically acceptable salt thereof wherein:

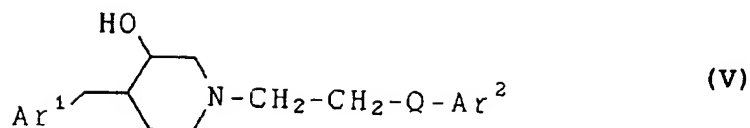
Ar<sup>1</sup> and Ar<sup>2</sup> are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an alkylguanidine group, a lower alkyl amino group or a lower alkoxy group; and

Q is -CH=CH- or -C≡C-.

12. A compound represented by the formula:



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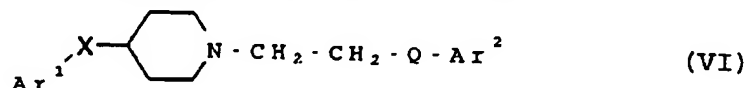


or a pharmaceutically acceptable salt thereof wherein:

Ar<sup>1</sup> and Ar<sup>2</sup> are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an alkylguanidine group, a lower alkyl amino group or a lower alkoxy group; and

Q is -CH=CH- or -C≡C-.

13. A compound represented by the formula:

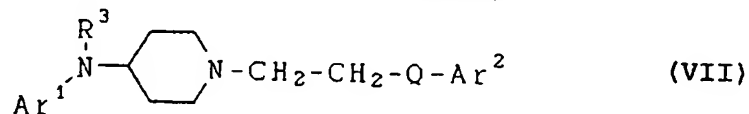


or a pharmaceutically acceptable salt thereof wherein:

Ar<sup>1</sup> and Ar<sup>2</sup> are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an alkylguanidine group, a lower alkyl amino group or a lower alkoxy group; X is O or S; and

Q is -CH=CH- or -C≡C-.

14. A compound represented by the formula:



or a pharmaceutically acceptable salt thereof wherein:

Ar<sup>1</sup> and Ar<sup>2</sup> are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc,

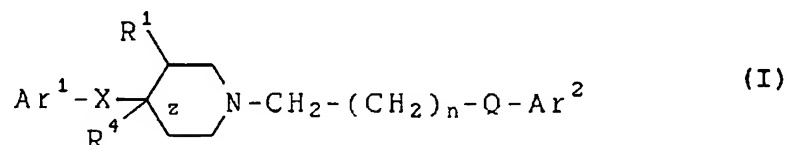
- 115 -

-NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an alkylguanidine group, a lower alkyl amino group or a lower alkoxy group; and

Q is -CH=CH- or -C≡C-; and

R<sup>3</sup> is hydrogen or a lower alkoxy group having 1 to 6 carbon atoms.

15. A method for treating disorders responsive to the selective blockade of N-methyl-D-aspartate receptor subtypes in an animal suffering thereof which comprises administering in unit dosage form of at least one compound represented by the formula:



or a pharmaceutically acceptable salt thereof wherein

Ar<sup>1</sup> and Ar<sup>2</sup> are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an alkylguanidine group, a lower alkyl amino group or a lower alkoxy group;

z is a single or double bond;

X is -(CHR<sup>2</sup>)<sub>m</sub>-, O, S or NR<sup>3</sup>, wherein each R<sup>2</sup> is independently hydrogen, hydroxy, lower alkoxy or a lower alkyl group having 1 to 6 carbon atoms and m is 0, 1 or 2, and R<sup>3</sup> is hydrogen or a lower alkyl group having 1 to 6 carbon atoms, provided that when z is a double bond then X is not O, S or NR<sup>3</sup>;

R<sup>1</sup> is hydrogen or hydroxy;

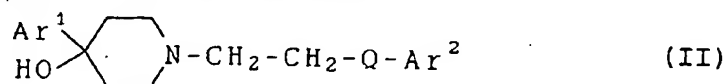
n is 0, 1 or 2;

Q is -CH=CH- or -C≡C-; and

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R<sup>4</sup> is hydrogen or hydroxy when z is a single bond, provided that when R<sup>4</sup> is hydroxy then R<sup>2</sup> is not hydroxy or alkoxy.

16. A method for treating disorders responsive to the selective blockade of N-methyl-D-aspartate receptor subtypes in an animal suffering thereof which comprises administering in unit dosage form of at least one compound represented by the formula:

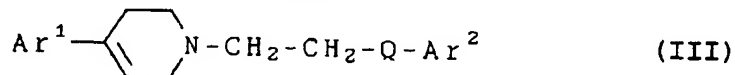


or a pharmaceutically acceptable salt thereof wherein:

Ar<sup>1</sup> and Ar<sup>2</sup> are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an alkylguanidine group, a lower alkyl amino group or a lower alkoxy group; and

Q is  $\text{--CH=CH--}$  or  $\text{--C=C--}$ .

17. A method for treating disorders responsive to the selective blockade of N-methyl-D-aspartate receptor subtypes in an animal suffering thereof which comprises administering in unit dosage form of at least one compound represented by the formula:

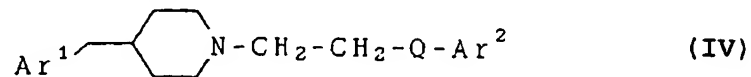


or a pharmaceutically acceptable salt thereof wherein:

Ar<sup>1</sup> and Ar<sup>2</sup> are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an alkylguanidine group, a lower alkyl amino group or a lower alkoxy group; and

Q is  $-\text{CH}=\text{CH}-$  or  $-\text{C}\equiv\text{C}-$ .

18. A method for treating disorders responsive to the selective blockade of N-methyl-D-aspartate receptor subtypes in an animal suffering thereof which comprises administering in unit dosage form of at least one compound represented by the formula:

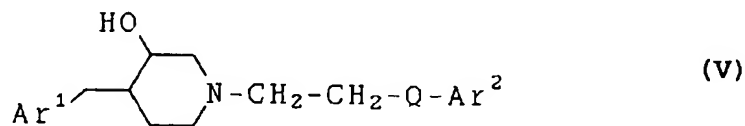


or a pharmaceutically acceptable salt thereof wherein:

$\text{Ar}^1$  and  $\text{Ar}^2$  are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group,  $-\text{NHAc}$ ,  $-\text{NHSO}_2\text{Me}$ ,  $-\text{N}(\text{SO}_2\text{Me})_2$ ,  $-\text{CONHalkyl}$ ,  $-\text{SO}_2\text{NH}_2$ , an alkylguanidine group, a lower alkyl amino group or a lower alkoxy group; and

Q is  $-\text{CH}=\text{CH}-$  or  $-\text{C}\equiv\text{C}-$ .

19. A method for treating disorders responsive to the selective blockade of N-methyl-D-aspartate receptor subtypes in an animal suffering thereof which comprises administering in unit dosage form of at least one compound represented by the formula:

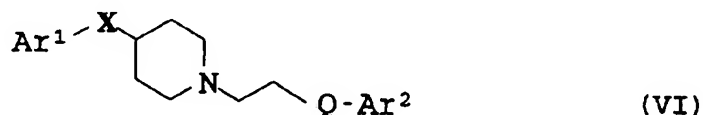


or a pharmaceutically acceptable salt thereof wherein:

$\text{Ar}^1$  and  $\text{Ar}^2$  are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group,  $-\text{NHAc}$ ,  $-\text{NHSO}_2\text{Me}$ ,  $-\text{N}(\text{SO}_2\text{Me})_2$ ,  $-\text{CONHalkyl}$ ,  $-\text{SO}_2\text{NH}_2$ , an alkylguanidine group, a lower alkyl amino group or a lower alkoxy group; and

Q is  $-\text{CH}=\text{CH}-$  or  $-\text{C}\equiv\text{C}-$ .

20. A method for treating disorders responsive to the selective blockade of N-methyl-D-aspartate receptor subtypes in an animal suffering thereof which comprises administering in unit dosage form of at least one compound represented by the formula:



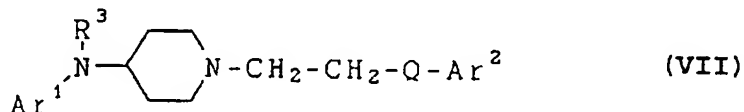
or a pharmaceutically acceptable salt thereof wherein:

Ar<sup>1</sup> and Ar<sup>2</sup> are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an alkyl guanidine group, a lower alkyl amino group or a lower alkoxy group;

Q is -CH=CH- or -C≡C-; and

X is O or S.

21. A method for treating disorders responsive to the selective blockade of N-methyl-D-aspartate receptor subtypes in an animal suffering thereof which comprises administering in unit dosage form of at least one compound represented by the formula:



or a pharmaceutically acceptable salt thereof wherein:

Ar<sup>1</sup> and Ar<sup>2</sup> are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an

alkylguanidine group, a lower alkyl amino group or a lower alkoxy group;

Q is  $-\text{CH}=\text{CH}-$  or  $-\text{C}\equiv\text{C}-$ ; and

$\text{R}^3$  is hydrogen or a lower alkoxy group having 1 to 6 carbon atoms.

22. A method for treating disorders responsive to the selective blockade of N-methyl-D-aspartate receptor subtypes in an animal suffering thereof which comprises administering in unit dosage form of at least one compound selected from the group consisting of:

1-[4-(3-Aminophenyl)-3-butynyl]-4-hydroxy-4-(4-chlorophenyl)piperidine;

1-((4-Phenyl)-3-butynyl)-4-hydroxy-4-phenylpiperidine;

1-[4-(3-Aminophenyl)-3-butynyl]-4-hydroxy-4-phenylpiperidine;

1-[4-(5-(2-Amino)pyridynyl)-3-butynyl]-4-hydroxy-4-(4-chlorophenyl)piperidine;

1-[4-(4-Fluorophenyl)-3-butynyl]-4-hydroxy-4-(4-chlorophenyl)piperidine;

1-[5-(3-Aminophenyl)-4-pentynyl]-4-hydroxy-4-(4-chlorophenyl)piperidine;

1-[4-(3-Aminophenyl)-3-butynyl]-4-(4-chlorophenyl)-1,2,5,6-tetrahydropyridine;

1-((4-Phenyl)-3-butynyl)-4-phenyl-1,2,5,6-tetrahydropyridine;

1-[4-(3-Aminophenyl)-3-butynyl]-4-phenyl-1,2,5,6-tetrahydropyridine;

1-[4-(5-(2-Amino)pyridynyl)-3-butynyl]-4-(4-chlorophenyl)-1,2,5,6-tetrahydropyridine;

1-[4-(4-Fluorophenyl)-3-butynyl]-4-(4-chlorophenyl)-1,2,5,6-tetrahydropyridine;

1-[5-(3-Aminophenyl)-4-pentynyl]-4-(4-chlorophenyl)-1,2,5,6-tetrahydropyridine;

4-Benzyl-1-[4-(3-aminophenyl)-3-butynyl]piperidine;

4-Benzyl-1-(4-phenyl-3-butynyl)piperidine;  
4-(4-Chloro)benzyl-1-[4-(3-aminophenyl)-3-butynyl]piperidine;  
4-(4-Chloro)benzyl-1-[4-(4-hydroxyphenyl)-3-butynyl]piperidine;  
4-(4-Chloro)benzyl-1-[4-(5-(2-amino)pyridynyl)-3-butynyl]-piperidine;  
1-[4-(4-Fluorophenyl)-3-butynyl]-4-(3-trifluoromethylbenzyl)-piperidine;  
4-(4-Chlorobenzyl)-1-[5-(3-aminophenyl)-4-pentynyl]-piperidine;  
4-Benzyl-1-[4-(3-aminophenyl)-3-butynyl]-3-hydroxypiperidine;  
4-Benzyl-1-(4-phenyl-3-butynyl)-3-hydroxypiperidine;  
4-(4-Chloro)benzyl-1-[4-(3-aminophenyl)-3-butynyl]3-hydroxypiperidine;  
4-(4-Chloro)benzyl-1-[4-(5-(2-amino)pyridynyl)-3-butynyl]-3-hydroxypiperidine;  
1-[4-(4-Fluorophenyl)-3-butynyl]-4-(3-trifluoromethylbenzyl)-3-hydroxy-piperidine;  
4-(4-Chlorobenzyl)-3-hydroxy-1-[5-(3-aminophenyl)-4-pentynyl]-piperidine;  
1-[4-(3-Aminophenyl)-3-butynyl]-4-phenoxy-piperidine;  
1-(4-Phenyl-3-butynyl)-4-phenoxy-piperidine;  
1-[4-(3-Aminophenyl)-3-butynyl]-4-(4-chloro)phenoxy-piperidine;  
1-[4-(5-(2-Amino)pyridynyl)-4-butynyl]-4-(4-chloro)phenoxy-piperidine;  
1-[4-(4-Fluorophenyl)-3-butynyl]-4-(3-trifluoromethyl)phenoxy-piperidine;  
1-[5-(3-Aminophenyl)-4-pentynyl]-4-(4-chloro)phenoxy-piperidine;  
1-[4-(3-Aminophenyl)-3-butynyl]-4-(phenyl)aminopiperidine;  
1-(4-Phenyl-3-butynyl)-4-(phenyl)aminopiperidine;

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1-[4-(3-Aminophenyl)-3-butynyl]-4-(4-chlorophenyl)aminopiperidine;  
1-[4-(5-(2-Amino)pyridynyl)-3-butynyl]-4-(4-chlorophenyl)aminopiperidine;  
1-[4-(4-Fluorophenyl)-3-butynyl]-4-(3-trifluoromethylphenyl)aminopiperidine; and  
1-[5-(3-Aminophenyl)-4-pentynyl]-4-(4-chlorophenyl)aminopiperidine;  
4-Phenyl-1-(4-phenyl-3-butynyl)piperidine;  
4-(3-(Trifluoromethyl)phenyl)-3-hydroxy-1-(4-phenyl-3-butynyl)piperidine;  
1-(4-(4-Aminophenyl)-3-butynyl)-4-(4-chlorophenyl)-4-hydroxypiperidine;  
N-n-Butyl-N'-(3-(4-(4-(4-chlorophenyl)-4-hydroxy)piperidinyl)butynyl)phenylguanidine;  
4-Benzyl-1-(4-(3-methylphenyl)-3-butynyl)piperidine;  
1-(4-(4-Aminophenyl)-3-butynyl)-4-benzylpiperidine;  
4-Benzyl-4-hydroxy-1-(4-phenyl-3-butynyl)piperidine;  
4-Benzyl-4-hydroxy-1-(4-(3-methylphenyl)-3-butynyl)piperidine;  
1-(4-(4-Aminophenyl)-3-butynyl)-4-benzyl-4-hydroxypiperidine;  
1-(4-(4-Aminophenyl)-3-butynyl)-4-(4-chlorobenzyl)piperidine;  
1-(4-(4-Amino-3-fluorophenyl)-3-butynyl)-4-(4-chlorobenzyl)piperidine;  
N-4-(1-(4-(3-Aminophenyl)butyn-3-yl)piperidinyl)-2-oxobenzimidazol;  
1-(4-(2-Aminophenyl)-3-butynyl)-4-phenylpiperidine;  
4-{4-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-but-1-ynyl}-phenylamine;  
N-{4-[4-(4-Phenoxy-piperidin-1-yl)-but-1-ynyl]-phenyl}-acetamide;



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4-{4-[4-(4-Methyl-benzyl)-piperidin-1-yl]-but-1-ynyl}-phenylamine;  
4-Benzyl-1-[4-(4-nitro-phenyl)-but-3-ynyl]-piperidine;  
4-Benzyl-1-[4-(4-methoxy-phenyl)-but-3-ynyl]-piperidine;  
4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenol;  
4-Benzyl-1-[4-(4-fluoro-phenyl)-but-3-ynyl]-piperidine;  
4-Benzyl-1-[4-(4-chloro-phenyl)-but-3-ynyl]-piperidine;  
4-Benzyl-1-[4-(3-chloro-phenyl)-but-3-ynyl]-piperidine;  
4-Benzyl-1-[4-(2,3-dichloro-phenyl)-but-3-ynyl]-piperidine;  
4-Benzyl-1-[4-(3,4-dichloro-phenyl)-but-3-ynyl]-piperidine;  
4-Benzyl-1-(4-p-tolyl-but-3-ynyl)-piperidine;  
4-Benzyl-1-[4-(2,3-dimethyl-phenyl)-but-3-ynyl]-piperidine;  
4-Benzyl-1-[4-(3,4-dimethyl-phenyl)-but-3-ynyl]-piperidine;  
3-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenylamine;  
3-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-benzylamine;  
N-{4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-acetamide;  
{4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-methyl-amine;  
{4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-dimethyl-amine;  
N-{4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-methanesulfonamide;  
4-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-benzamide;

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N- (Methylsulfonyl) -N- [4- [4- [4- (phenylmethyl) -1-piperidinyl] -1-butynyl]phenyl] -methanesulfonamide;

4- [4- (4-Benzyl-piperidin-1-yl) -but-1-ynyl] -benzenesulfonamide;

4- [4- (4-Benzyl-piperidin-1-yl) -but-1-ynyl] -N-butyl-benzamide;

1- (4-Benzo[1,3]dioxol-5-yl-but-3-ynyl) -4-benzyl-piperidine;

4-Benzyl-1- [4- (2,3-dihydro-benzo[1,4]dioxin-6-yl) -but-3-ynyl] -piperidine;

4- [3- (4-Benzyl-piperidin-1-yl) -prop-1-ynyl] -phenylamine;

N- {4- [3- (4-Benzyl-piperidin-1-yl) -prop-1-ynyl] -phenyl} -methanesulfonamide;

N- {4- [4- (4-Phenylsulfanyl-piperidin-1-yl) -but-1-ynyl] -phenyl} -acetamide;

5- [4- (4-Benzyl-piperidin-1-yl) -but-1-ynyl] -1H-indole;

4- {4- [4- (4-Methyl-benzyl) -piperidin-1-yl] -but-1-ynyl} -phenol;

5- [4- (4-Benzyl-piperidin-1-yl) -but-1-ynyl] -1H-indazole;

4- [4- (4-Benzyl-piperidin-1-yl) -but-1-ynyl] -2-nitro-phenylamine;

4- [4- (4-Benzyl-piperidin-1-yl) -but-1-ynyl] -benzene-1,2-diamine;

5-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-1,3-dihydro-benzoimidazol-2-one;

N-{4-[4-(4-Phenylsulfanyl-piperidin-1-yl)-but-1-ynyl]-phenyl}-methanesulfonamide;

4-[3-(4-Benzyl-piperidin-1-yl)-prop-1-ynyl]-benzamide;

4-[3-(4-Benzyl-piperidin-1-yl)-prop-1-ynyl]-benzenesulfonamide;

5-[4-(4-Benzyl-piperidin-1-yl)-but-1-ynyl]-1H-indole-2,3-dione;

4-benzyl-4-hydroxy-1-(4-3-methylphenyl)-3-butynyl)piperidine;

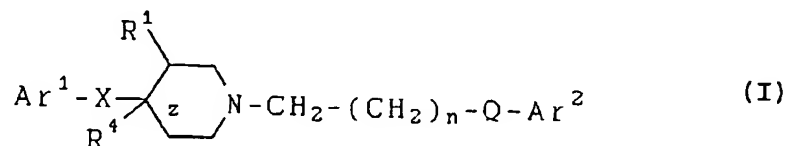
4-benzyl-4-hydroxy-1-(4-phenyl-3-butynyl)piperidine;

4-benzyl-4-hydroxy-1-(4-(4-aminophenyl)-3-butynyl)piperidine; and

4-(4-methylbenzyl)-4-hydroxy-1-(4-(4-aminophenyl)-3-butynyl)piperidine, and

a pharmaceutically acceptable salt thereof.

23. A method for preparing the compound represented by formula I:



or a pharmaceutically acceptable salt thereof wherein Ar<sup>1</sup> and Ar<sup>2</sup> are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc,

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-NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an alkylguanidine group, a lower alkyl amino group or a lower alkoxy group;

z is a single or double bond;

X is -(CHR<sup>2</sup>)<sub>m</sub>-, O, S or NR<sup>3</sup>, wherein each R<sup>2</sup> is independently hydrogen, hydroxy, lower alkoxy or a lower alkyl group having 1 to 6 carbon atoms and m is 0, 1 or 2, and R<sup>3</sup> is hydrogen or a lower alkyl group having 1 to 6 carbon atoms, provided that when z is a double bond then X is not O, S or NR<sup>3</sup>;

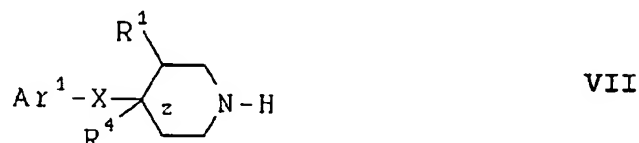
R<sup>1</sup> is hydrogen or hydroxy;

n is 0, 1 or 2;

Q is -CH=CH- or -C≡C-; and

R<sup>4</sup> is hydrogen or hydroxy when z is a single bond, provided that when R<sup>4</sup> is hydroxy then R<sup>2</sup> is not hydroxy or lower alkoxy, said method comprising the steps of:

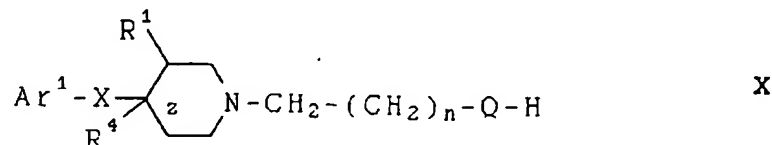
(a) reacting, in the presence of a base, a compound of formula VII



wherein Ar<sup>1</sup>, X, R<sup>1</sup>, R<sup>4</sup> and z are as previously described, with a compound of formula IX



wherein n and Q are as previously described and L is a leaving group to afford a compound of formula X



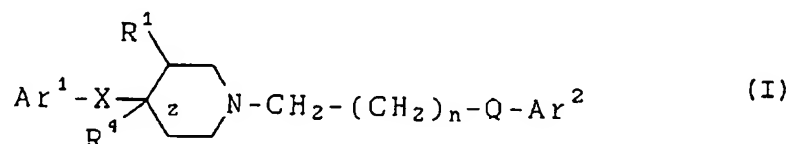
wherein Ar<sup>1</sup>, X, R<sup>1</sup>, R<sup>4</sup>, z, n and Q are as previously described; and

(b) reacting the compound of formula X with Ar<sup>2</sup>Y, wherein Ar<sup>2</sup> is as previously defined and Y is a

transmetalation group, in the presence of a palladium catalyst to afford the compound of formula I.

24. A method according to claim 23, wherein said transmetalation group is selected from the group consisting of Br, I, B(OH)<sub>2</sub> and HgCl.

25. A method for preparing the compound represented by formula I:



or a pharmaceutically acceptable salt thereof wherein

Ar<sup>1</sup> and Ar<sup>2</sup> are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, an alkylguanidine group, a lower alkyl amino group or a lower alkoxy group;

z is a single or double bond;

X is -(CHR<sup>2</sup>)<sub>m</sub>-, O, S or NR<sup>3</sup>, wherein each R<sup>2</sup> is independently hydrogen, hydroxy, lower alkoxy or a lower alkyl group having 1 to 6 carbon atoms and m is 0, 1 or 2, and R<sup>3</sup> is hydrogen or a lower alkyl group having 1 to 6 carbon atoms, provided that when z is a double bond then X is not O, S or NR<sup>3</sup>;

R<sup>1</sup> is hydrogen or hydroxy;

n is 0, 1 or 2;

Q is -CH=CH- or -C≡C-; and

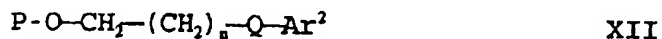
R<sup>4</sup> is hydrogen or hydroxy when z is a single bond, provided that when R<sup>4</sup> is hydroxy then R<sup>2</sup> is not hydroxy or lower alkoxy, said method comprising the steps of:

(a) reacting, in the presence of a palladium catalyst, a compound of formula XI

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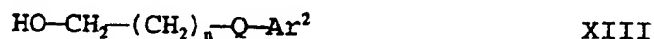


wherein P is a general protecting group, and n and Q are as previously described, with  $Ar^2Y$ , wherein  $Ar^2$  is as previously defined and Y is a transmetalation group, to afford a compound represented by formula XII



wherein P, n, Q and  $Ar^2$  are as previously described;

(b) deprotecting the compound of formula XII to give a compound represented by formula XIII



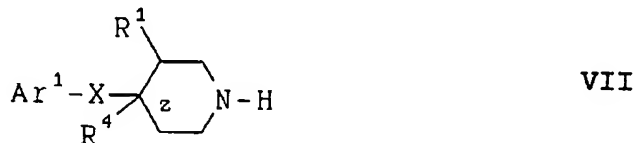
wherein n, Q and  $Ar^2$  are as previously described;

(c) reacting the compound of formula XIII with an activating compound, in the presence of base, to give the compound represented by formula XIV



wherein A is an activating group, and n, Q and  $Ar^2$  are as previously described; and

(d) reacting, in the presence of a base, the compound of formula XIV with the compound of formula VII



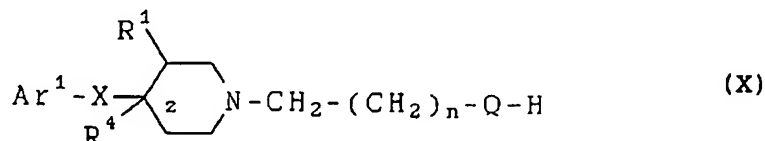
wherein  $Ar^1$ , X,  $R^1$ ,  $R^4$  and z are as previously described, to give the compound of formula I.

26. A method according to claim 25, wherein said transmetalation group is selected from the group consisting of Br, I,  $B(OH)_2$  and  $HgCl$ .

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27. A method according to claim 26, wherein said activating compound is selected from the group consisting of tosylates, triflates, mesylates and diethylazadicarboxylate.

28. A compound represented by the formula (X)



or a salt thereof, wherein

Ar<sup>1</sup> is aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, a lower alkyl amino group or a lower alkoxy group;

z is a single or double bond;

X is -(CHR<sup>2</sup>)<sub>m</sub>-, O, S or NR<sup>3</sup>, wherein each R<sup>2</sup> is independently hydrogen, hydroxy, lower alkoxy or a lower alkyl group having 1 to 6 carbon atoms and m is 0, 1 or 2, and R<sup>3</sup> is hydrogen or a lower alkyl group, provided that when z is a double bond then X is not O, S or NR<sup>2</sup>;

Q is -CH=CH- or -C=C-;

R<sup>1</sup> is hydrogen or hydroxy; and

R<sup>4</sup> is hydrogen or hydroxy when z is a single bond, provided that (i) when X is -(CHR<sup>2</sup>)<sub>m</sub>-, m is 0 and Q is -C=C- then z is not a double bond and (ii) when R<sup>4</sup> is hydroxy then R<sup>2</sup> is not hydroxy or lower alkoxy.

29. A compound according to claim 28, said compound selected from the group consisting of

1-(3-Butynyl)-4-hydroxy-4-phenylpiperidine;

1-(3-Butynyl)-4-hydroxy-4-((4-chloro)phenyl)piperidine;

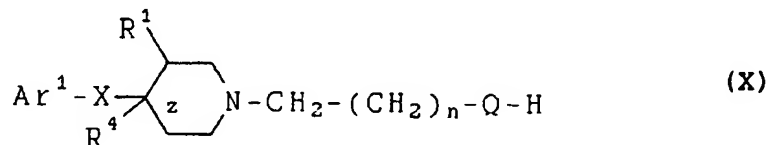
1-(3-Butynyl)-4-hydroxy-4-((3-trifluoromethyl)phenyl)piperidine;  
4-Hydroxy-4-phenyl-1-(2-propynyl)piperidine;  
4-Hydroxy-1-(4-pentynyl)-4-phenylpiperidine;  
1-(3-Butynyl)-4-(4-chloro)phenyl-1,2,5,6-tetrahydropyridine;  
1-(3-Butynyl)-4-(4-trifluoromethyl)phenyl-1,2,5,6-tetrahydropyridine;  
4-(4-Chloro)phenyl-1-(2-propynyl)-1,2,5,6-tetrahydropyridine;  
4-(4-Chloro)phenyl-1-(4-pentynyl)-1,2,5,6-tetrahydropyridine;  
4-Benzyl-1-(3-butynyl)piperidine;  
4-(4-Chloro)benzyl-1-(3-butynyl)piperidine;  
4-(3-Trifluoromethyl)benzyl-1-(3-butynyl)piperidine;  
4-(4-Chloro)benzyl-1-(2-propynyl)piperidine;  
4-(4-Chloro)benzyl-1-(4-pentynyl)piperidine;  
4-Benzyl-1-(3-butynyl)-3-hydroxy-piperidine;  
4-(4-Chloro)benzyl-1-(3-butynyl)-3-hydroxy-piperidine;  
4-(3-Trifluoromethyl)benzyl-1-(3-butynyl)-3-hydroxy-piperidine;  
4-(4-Chloro)benzyl-3-hydroxy-1-(2-propynyl)piperidine;  
4-(4-Chloro)benzyl-3-hydroxy-1-(4-pentynyl)piperidine;  
1-(3-Butynyl)-4-phenoxy-piperidine;  
1-(3-Butynyl)-4-(4-chloro)phenoxy-piperidine;  
1-(3-Butynyl)-4-(3-trifluoromethyl)phenoxy-piperidine;  
4-(4-Chloro)phenoxy-1-(2-propynyl)piperidine;  
1-(4-Pentynyl)-4-(4-chloro)phenoxy-piperidine;  
1-(3-Butynyl)-4-(phenyl)aminopiperidine;  
1-(3-Butynyl)-4-((4-chloro)phenyl)aminopiperidine;  
1-(3-Butynyl)-4-((3-trifluoromethyl)phenyl)aminopiperidine;



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4-((4-Chloro)phenyl)amino-1-(2-propynyl)piperidine;  
 1-(4-Pentynyl)-4-((4-chloro)phenyl)aminopiperidine;  
 1-(But-3-ynyl)-4-(4-chlorobenzyl)piperidine;  
 4-Benzyl-1-(but-3-yn-1-yl)-4-hydroxypiperidine; 4-4-(4-Methylbenzyl)-4-hydroxy-1-(but-3-yn-1-yl)piperidine;  
 and a salt thereof.

30. A method for treating disorders responsive to the selective blockade of N-methyl-D-aspartate receptor subtypes in an animal suffering thereof which comprises administering in unit dosage form of at least one compound represented by the formula (X):



or a pharmaceutically acceptable salt thereof, wherein

Ar<sup>1</sup> is aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, -NHSO<sub>2</sub>Me, -N(SO<sub>2</sub>Me)<sub>2</sub>, -CONHalkyl, -SO<sub>2</sub>NH<sub>2</sub>, a lower alkyl amino group or a lower alkoxy group;

z is a single or double bond;

X is -(CHR<sup>2</sup>)<sub>m</sub>-, O, S or NR<sup>3</sup>, wherein each R<sup>2</sup> is independently hydrogen, hydroxy, lower alkoxy or a lower alkyl group having 1 to 6 carbon atoms and m is 0, 1 or 2, and R<sup>3</sup> is hydrogen or a lower alkyl group

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having 1 to 6 carbon atoms, provided that when z is a double bond then X is not O, S or NR<sup>2</sup>;

Q is  $\text{—CH=CH—}$  or  $\text{—C}\equiv\text{C—}$ ;

R<sup>1</sup> is hydrogen or hydroxy; and

R<sup>4</sup> is hydrogen or hydroxy when z is a single bond, provided that (i) when X is  $\text{—(CHR}^2\text{)}_m\text{—}$ , m is 0 and Q is  $\text{—C}\equiv\text{C—}$  then z is not a double bond and (ii) when R<sup>4</sup> is hydroxy then R<sup>2</sup> is not hydroxy or lower alkoxy.

31. The method according to any one of claims 15-22 and 30, wherein said disorder is stroke, cerebral ischemia, central nervous system trauma or hypoglycemia.

32. The method according to any one of claims 15-22 and 30, wherein said disorder is anxiety, convulsions or chronic pain.

33. The method according to any one of claims 15-22 and 30, wherein said disorder is a aminoglycoside antibiotics-induced hearing loss.

34. The method according to any one of claims 15-22 and 30, wherein said disorder is Parkinson's disease.

35. The method according to any one of claims 15-22 and 30, wherein said disorder is a migraine headache.

36. The method according to any one of claims 15-22 and 30, wherein said disorder is glaucoma or CMV retinitis.

37. The method according to any one of claims 15-22 and 30, wherein said disorder is a psychosis.

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38. The method according to any one of claims 15-22 and 30, wherein said disorder is urinary incontinence.

39. The method according to any one of claims 15-22 and 30, wherein said disorder is opioid tolerance or withdrawal.

40. The method according to any one of claims 15-22 and 30, wherein said disorder is aminoglycoside antibiotics-induced hearing loss.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/20766

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/221, 255, 258, 311, 312, 321, 322; 540/500, 506, 518; 544/283, 285, 349; 546/153, 199, 201

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS, APS, DIALOG

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US, A, 3,686,187, (COLE ET AL) 22 AUGUST 1972, see entire document.	1, 3-6, 8, 11, 14, 15, 18, 21 ----- 23-27
X — Y	US, A, 4,567,186, (BANNO ET AL) 28 JANUARY 1986, see entire document.	1, 3-6, 8, 11, 15, 18 ----- 23-27
X — Y	US, A, 4,577,020 (GALL) 18 MARCH 1986, see entire document.	1, 3-6, 8, 11, 15, 18 ----- 23-27

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

20 MARCH 1997

Date of mailing of the international search report

6 MAY 1997

Name and mailing address of the ISA/US  
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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/20766

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US, A, 3,311,624 (OHNACKER ET AL.) 28 MARCH 1967, see entire document.	28, 30, 31, 32, 35, 37 ----- 33, 34, 36, 38-40
X -- Y	US, A, 4,312,876 (KLIOZE ET AL) 26 JANUARY 1982, see entire document.	28, 30-32, 35, 37 ----- 33, 34, 36, 38-40
X -- Y	DE, A, 2,539,452, (ELI LILLY AND CO) 12 MARCH 1976, see entire document.	1, 3-6, 8, 11, 15, 18 ----- 23-27
X -- Y	DE, A, 3,421,641 (MERCK ) 12 DECEMBER 1985, see entire document.	1, 3-6, 8, 10, 11, 15, 18 ----- 17, 23-27
X	Chemical Abstracts, volume 94, No. 15, issued 13 April 1981, Praliev et al. "Synthesis of piperidine and decahydroquinoline derivatives, their analgesic and psychotropic properties" see pages 673, column 1, abstract No. 94:121260j. Khim.-Farm. Zh. 14(10), 37-40.	1, 3-6, 8, 9, 11, 15, 16, 18
X	Chemical Abstracts, volume 115, No. 23, issued 09 December 1991, Srulovitch et al. "4-phenylamidopiperidines, synthesis, pharmacological testing and SAR analysis" page 18, column 1, abstract No. 115:247459b	28
Y	Chemical Abstracts, volume 120, No. 25, issued 20 June 1994, Yang, et al. "Synthesis and anesthetic activity of 3-methyl fentanyl derivatives" page 880, abstract No. 120:323214p	1-8, 14, 15, 21, 22, 28, 29, 30- 32, 35, 37
Y	A. Burger, "A GUIDE TO THE CHEMICAL BASIS OF DRUG DESIGN" Published 1983, by WILEY INTERSCIENCE (N.Y.) see page 15.	1-8, 14, 15, 21, 22, 28, 29, 30- 32, 35, 37
Y	Chemical Abstracts, volume 101, No. 7, issued 13 AUGUST 1984, Praliev et al. "Synthesis of piperidine and decahydroquinoline derivatives, their analgesic and psychotropic properties." page 603, column 1, abstract No. 101:54881k, Khim-Farm. Zh. 17(9)1053-9	1-8, 14, 15, 21, 22, 28, 29, 30- 32, 35, 37

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/20766

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/20766

## A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A61K 31/445, 31/47, 31/495, 31/55, 31/505; C07D 215/16, 239/72, 241/36, 243/10, 234/12, 243/24, 401/06, 403/06, 413/06

## A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/221, 255, 258, 311, 312, 321, 322; 540/500, 506, 518; 544/283, 285, 349; 546/153, 199, 201

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-27, drawn to compounds, compositions, method of using and method of making the compounds.  
Group II, claims 28-30, drawn to intermediates which have independent use and their compositions.  
Group III, claim 31 drawn to method of treating stroke, cerebral ischemia.....using compounds;  
Group IV, claim 32, drawn to method of treating anxiety; convulsion and chronic pain...using compounds;  
Group V, claim 33 or claim 40 (please note that claim 33 and 40 are duplicates), drawn to method of aminoglycoside antibiotics-induced hearing loss;  
Group VI, claim 34, drawn to method of treating Parkinson's disease...using compounds;  
Group VII, claim 35, drawn to method of treating migraine headache.  
Group VIII, claim 36, drawn to method of treating glaucoma or CMV retinitis...using compounds;  
Group IX, claim 37, drawn to method of treating psychoses...using compounds;  
Group X, claim 38, drawn to method of treating urinary incontinence using compounds.  
Group XI, claim 39, drawn to method of treating opioid tolerance or withdrawal using compounds.

The inventions listed as Groups I-XI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Compounds of Groups I and II are independent and distinct. Compounds of group II can be used to make compounds of group I, in addition, each group I and group II compounds have independent utility, therefore, groups I and II do not share the same special technical feature.

Process of using compounds as groups III-XI must be searched and examined independently since the allowable combination of different categories under PCT Rule 13.1 and 13.2 are:

- a) A product and a process specially adapted for the manufacture of said product;
  - b) A product and a process of use of said product;
  - c) A product, a process specially adapted for the manufacture for the said product and a use of the said product;
  - d) A process and an apparatus or means specifically designed for carrying out the said process;
  - e) A product, a process specially adapted for the manufacture of the said product and an apparatus or means specifically designed for carrying out the said process;
- and the additional independent process of treating the diversified diseases lacks unity of invention.